Imaging the aging brain:

Cognitive and electrophysiological correlates

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CONTENTS

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Oslo, July 27th 2010

BACKGROUND

The epistemological notion that the human mind can be studied and characterized in terms of biological processes and mechanisms is generally undisputed among psychologists and cognitive scientists. Bodily sensations, perceptions, thoughts and feelings are all caused by neurobiological processes in the brain subserved and restricted by a highly complex interplay between various levels of cortical and subcortical neurocircuitry. Seminal studies of patients suffering from specific damages to the brain (e.g. Damasio et al., 1994; Mesulam, 1981; Scoville & Milner, 1957) have played an integral part in linking the cognitive, emotional and behavioral domains, i.e. the mind, to the workings of the brain, and have paved the way towards the by now highly influential synthesis of the cognitive and neurosciences (Gazzaniga, 2004).

However, any progress within the life sciences will ultimately be restricted by methodological and technological constraints. In the case of the cognitive neurosciences, these technological constraints have mainly been related to the challenges met when performing research on the living human brain. Ethical considerations have to a large degree precluded invasive investigations, and most knowledge about the interplay between brain and behavior has been produced within a comparative animal research setting. Comparative research programs have and are still yielding important and powerful information. However, the relations between e.g. rodent and primate behaviour and cerebral systems on one side, and human cognition and neurocircuitry on the other side are complex and not fully understood. The last couple of decades have yielded important methodological advances in brain imaging techniques, in particular within the field of magnetic resonance imaging (MRI). The window into the functional and structural architecture of the brain provided by advanced neuroimaging techniques have now made it possible to track the structural and functional correlates of the brain at work, and have thus provided an unprecedented opportunity to study the biological basis of the human mind. These advances have implied that what was recently only within sight for the cognitive and neuroscience communities is now within grasp.

Figure 1 shows a schematic summary of selected available imaging techniques, and highlights the methods used in the present thesis as well as the level of information provided by the different methods. A fundamental differentiation can be made between structural and functional brain imaging methods. Structural neuroimaging allows the researcher to make inferences about various aspects of the structural makeup of the brain. Available analysis methods enable detailed estimates of the volume of neuroanatomical structures (e.g. the

hippocampus), the thickness of the cerebral cortex or inferences about the microstructural properties of the nerve fibers connecting the various structures and regions of the brain. The level of detail and throughput provided by such analysis methods are well beyond what can be achieved by conventional neuroradiological examinations, and it is therefore now possible to quantify individual differences in various components of the structural makeup of the brain in large groups of individuals within a reasonable amount of time.

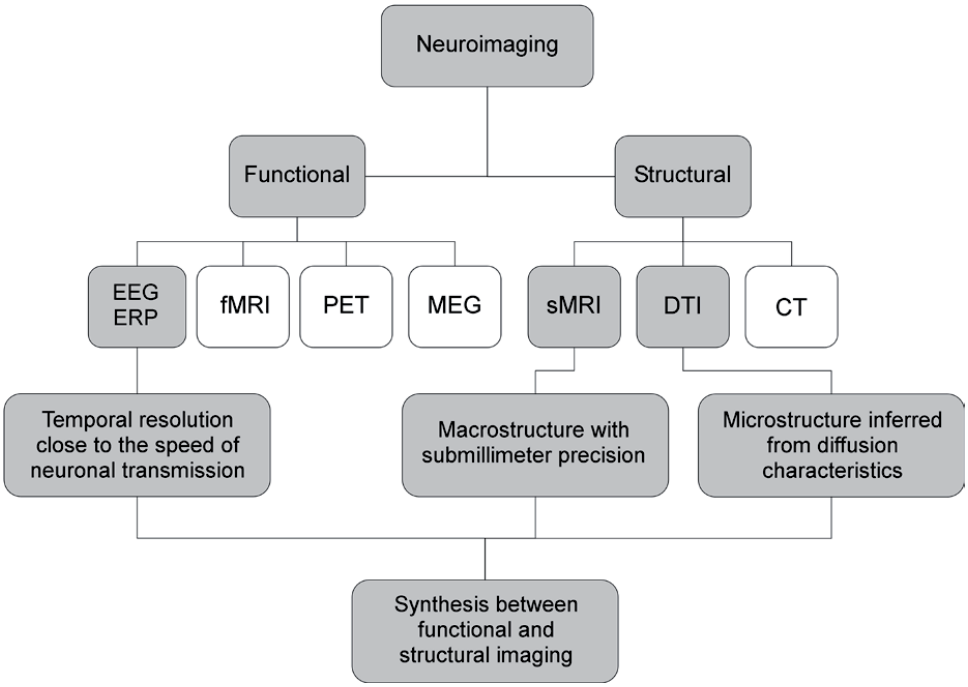

FIGURE 1: Selected available neuroimaging techniques. The shaded boxes mark the methods used in the present thesis and the possible level of interpretation provided by each method. The main objective of the present thesis is to contribute to the bridging between various neuroimaging techniques and cognition by providing converging evidence from a multimodal methodological perspective. EEG: electroencephalography, ERP: event-related potentials, fMRI: functional magnetic resonance imaging, PET: positron emission tomography, MEG: magnetoencephalography, sMRI: structural magnetic resonance imaging, DTI: diffusion tensor imaging, CT: computerised tomography.

These technological and analytical advances in structural neuroimaging have enabled large-scale studies aiming at indentifying structural properties of the brain that typically are associated with for example healthy or "optimal" aging (e.g. which structural properties differentiates between high and low performing subjects?), cognitive decline (e.g. which structural measures are most closely related to decreased memory performance) or various psychiatric or neurodegenerative disorders (e.g. how is the brain of an Alzheimer's patient different from the brain of an age-matched healthy peer?). In this thesis we have investigated macro- and microstructrual properties of the brain using cortical and subcortical morphometry and diffusion tensor imaging, respectively.

While structural imaging methods relate to the details of the brain's structural makeup, functional imaging is sensitive to alterations in the activation patterns of the brain as a function of time. In the present thesis we have used event-related potentials derived from continuous recordings of the individual electroencephalography during task performance. Event-related potentials provide a measure of the spatiotemporal pattern of electrical activity recorded from the subject's scalp on a temporal scale within milliseconds. The pattern relates to a certain event, for example a motor execution or a decision, and the fine-grained temporal resolution enables the researcher to track the sequential dynamics leading to and preceding the event. The exact neurophysiological underpinnings of the electroencephalography are unknown, but it is assumed to reflect large-scale functional integration of neuronal networks, and the method thus provide a window into the ongoing synchronous brain activity and the transient alterations associated with a specific event (please see Methods for more details on the imaging methods applied)

Research integrating cognitive and imaging data seeks to elucidate underlying mechanisms by way of biomarkers and intermediate phenotypes. Biomarkers and phenotypes are physical traits or measurable biologically produced changes in the body, and might be physiological, cognitive, psychological or neuroanatomical in nature. Intermediate phenotypes are measurable components between for example a disease and a distal genotype, they are less complex correlates of the disorder than are clinical symptoms and are putatively more closely related to gene action and/or brain function (Gottesman & Gould, 2003). However, even the most precise molecular or genetic data might prove irrelevant if the phenotypes (e.g. cognitive or imaging data) are insensitive.

Within the emerging field of the cognitive neurosciences, a common limitation hampering the interpretations and generalisations of results is that while the tests might be standardised and shown to separate between clinical groups and healthy controls, they often

lack a strong conceptual and theoretical association to fundamental brain function. Therefore, studies aiming to validate cognitive and imaging phenotypes are valuable (see e.g. Sabb et al., (2009) for a recent meta-analysis and discussion of memory and intelligence as cognitive phenotypes). Here, strong theory-driven operationalizations based on cognitive theory in combination with knowledge about brain function are *sine qua nons*. Indeed, leading researchers within the field of the social and cognitive neurosciences have proposed that a proper understanding of the functional and structural organization of the human brain demands an expansion of the range of the psychological sciences beyond a science of behavior, and beyond a science of the mind, to include a science of the brain (Cacioppo & Decety, 2009).

The main objective in the present thesis has been to investigate and establish the links between structural and functional brain imaging measures and specific cognitive functions within the perspective of the aging brain and mind. The studies presented in this thesis should thus partly be seen as an attempt to answer the call to integrate the cognitive and psychological sciences with a science of the brain. To this end, we have used specific cognitive tests that have been developed based on both cognitive theory and assumptions about the workings of the brain, and which have repeatedly been validated using a wide array of methodological approaches, including electrophysiological, behavioral, clinical, functional and structural magnetic resonance imaging, genetic and lesion data (see Methods section below). We have utilized individual differences in performance on these experimental tests as a source of cognitive and behavioral information, and have sought to detect the macro- and microstructural brain variables underlying this variation in a large sample of healthy volunteers.

Although the main focus in this thesis has been on individual differences in a healthy population and normal cognitive variation, this work is not without clinical implications. It is now largely accepted that some common mild disorders might merely be the quantitative extreme manifest of the same factors that create normal variation, and that there therefore might not exist any common disorders, just dimensions of normal variation (Plomin & Kosslyn, 2001). This dimensional perspective has its limitations, for example for Alzheimer's disease which likely exhibits neuropathological processes distinct from normal aging (see e.g. Buckner, 2004; Buckner et al., 2005; Frisoni et al., 2010; Sperling et al., 2010; Thompson et al., 2003). However, the dimensional understanding of the shaded pathways from normal to abnormal functioning, i.e. from health to disease, creates a philosophical and empirical framework from which to interpret and understand the findings in the present thesis. With the

ultimate goal to contribute to the understanding of the pathophysiological mechanisms in cognitive decline and neurodegeneration, the clinical focus in the thesis is aimed at increasing the knowledge of the brain structural, functional and cognitive consequences of normal aging, and how the relationships between phenotypes of brain structure and function changes with age. Currently, 36 million people worldwide are living with a diagnosis of dementia. This number is projected to double in 20 years, leading to at least 66 million patients in 2030 (Bettens et al., 2010). Hence, age-related cognitive impairment and dementia pose huge challenges to healthcare, and require large research efforts investigating the causes and consequences of brain aging.

Although still a matter of investigation and debate (Schaie, 2009), aging is assumed to be associated with cognitive decline (Salthouse, 2009), but not uniformly across functions (Hedden & Gabrieli, 2004) or individuals. Older adults are in general slower (Salthouse, 1996) and have reduced working memory capacity compared to their younger counterparts (Dobbs & Rule, 1989). However, the individual variability is gross. While some individuals show steep and progressive cognitive decline as they get older, others show only moderate losses. The underlying cause(s) of such individual variation in age-related cognitive decline is a key to the understanding of the pathophysiology of neurodegenerative disease (Bartzokis, 2004; Raz & Rodrigue, 2006). One approach for delineating such variation is to use neuroimaging techniques to associate variability in brain structure to variability in cognitive functions. Although the associations between brain structure and cognition are far from simple, it is known that e.g. decreases in cognitive functions among healthy older adults is paralleled by concurrent age-related reductions in brain volume, thinning of the cerebral cortical ribbon and expansion of the ventricular compartments (Fjell et al., 2009; Fotenos et al., 2005; Jernigan et al., 2001; Raz et al., 2005; Resnick et al., 2003; Salat et al., 2004; Sowell et al., 2003; Walhovd et al., in press). Stereological studies have documented significant morphological alterations and loss of dendritic spines in cortical pyramidal cells, which might impose post-synaptic effects on several neurotransmitter systems. Such alterations render neurons more vulnerable to impaired transmission and thus disrupts the corticocortical signalling pathways and effectively causing cognitive decline (Dickstein et al., 2007). However, as discussed, despite these general trends, there is ample evidence of considerable variability between individuals. An important task for the cognitive neurosciences is to understand the biological basis of this individual variability by untangling the associations between brain structure, brain function and cognition in the aging brain (Reuter-Lorenz & Park, 2010).

Previous studies in general converge on a positive association between general neuropsychological functions and the structural integrity of the brain, for example as indexed by the thickness of the cerebral cortex (Chee et al., 2009; Dickerson et al., 2008; Fjell et al., 2006; Narr et al., 2007; Shaw et al., 2006). However, it has not been known to which degree similar relationships might be found for more specific experimentally assessed attentional functions or electrophysiological measures of brain function independent of more general neuropsychological and intellectual abilities. This is an important question because it puts the notion of specific regional relationships between brain structure, brain function and cognition to test.

Aging is not a disease. However, by applying a dimensional perspective, aging provides a model of the changes associated with neurodegenerative disorders like Alzheimer's disease. Thus, a deeper understanding of how the brain changes with normal aging and further how these changes influence cognitive functions might prove instrumental in facilitating targeted interventions in prevention and treatment of disease. Neurons in the brain are affected by similar age-related factors as cells in other body organs, including e.g. increasing oxidative stress, accumulation of damaged proteins, nucleic acid lesions and altered energy homeostasis (Mattson & Magnus, 2006). In some individuals, neurobiological changes seen during the course of normal aging accelerates in selected neuronal populations, effectively contributing to the development of cognitive decline and dementia. Hence, whether the individual will develop a neurodegenerative disease during the course of aging is determined by a dynamic interplay between environmental and genetic factors imposing either positive or negative impacts on the normal molecular and cellular processes of aging (Mattson & Magnus, 2006).

Summarized, individual differences in cognitive functions and strategies are likely related to brain activation patterns that differ qualitatively among individuals, and which are under genetic control (Koten et al., 2009). Both environmental and genetic factors vary between individuals, and this variation modulates both individual differences in cognitive functions and the risk of developing a neurodegenerative disease. Consequently, describing and understanding the aging-related alterations in the healthy human brain, and the mechanisms that produce individual differences, provide a window into the processes that at a later stage might accelerate and produce symptoms characteristic for neurodegeneration, including cognitive decline.

It is generally assumed that the efficient neuronal transmission and integrated brain activity underlying cognitive processing are dependent upon the quality of the fiber pathways

connecting the relevant regions of the brain. In the first study, we tested the associations between an imaging biomarker of the microstructural properties of the white matter pathways wiring the brain and an electrophysiological marker of cognitive processing in response to commission errors in a speeded response task. We anticipated that individuals showing a strong electrophysiological response, as an indicator of efficient transient large-scale neuronal integration, would also show more coherent fiber networks in relevant areas. Such a finding could provide a link between two widely used imaging techniques, and thus serve to validate the typical biological interpretations derived from these measures. The findings from this study indicated a link between the structural properties of the white matter pathways and brain activity, providing encouraging evidence of an association between the structural connectivity and functional integration within the same neuronal network.

Interestingly, the ability to non-invasively and reliably characterize the structural and functional organization of the living human brain has led to the emergent idea of the brain as a plastic structure being sculpted by a combination of environmental, experience-related and genetic factors. However, despite the optimistic view proposed by some researchers in the field, it has also become evident that the brain changes and deteriorates as we grow older, and further that these changes likely are causing, or at the very least are related to, the cognitive decline experienced by some elderly individuals.

As discussed above, the variability between individuals is large, and while some individual age “gracefully”, others show severe functional decline. In order to understand and ultimately detect, limit and treat cognitive impairment in aging, more knowledge about the normal age-related changes are needed. An important task for the neurosciences is therefore to characterize and understand the factors underlying age-related changes in the structural and functional organization of the brain. The findings from Paper I taught us that subtle differences in the quality of the brain wiring are associated with the degree of large-scale functional integration of brain activity. However, how this underlying structural makeup changes throughout life has not been known, a question which has important implications for cognitive neurodevelopment and aging.

Therefore, in the second study we sought to describe the age-related patterns of change in the microstructural properties of the white matter pathways in the brain, and further compared these trajectories to the trajectories of the volume of the various structures. Interestingly, the results indicated that the microstructure of the pathways showed strong effects of age, and further that the quality of the wires showed evidence of a three-phasic pattern throughout the lifespan, with accelerating alterations in the first and last part of life,

with an intermediate phase of relative stability. These patterns bare resemblance to what is known about lifespan cognitive development, and, despite several limitations discussed below, the findings thus further support the use of imaging derived microstructural properties in studies aiming to integrate various levels of imaging and cognitive phenotypes.

Lesion studies have consistently shown that damages to specific areas of the brain produce characteristic and differentiated behavioral and cognitive consequences. It is therefore assumed that specific cognitive functions are subserved by specific cortical networks. Therefore, subtle structural differences in these specific cortical regions are expected to be associated with corresponding differences in cognitive functions. However, since previous structural imaging studies have usually focused on the associations between brain structure and general intellectual abilities or cognitive decline as measured by non-specific clinical screening instruments, it has not been known to which degree experimental neurocognitive assessment tools and advanced neuroimaging methods converge on the level of regional specificity.

The findings from Paper I in this thesis supported the notion of localized relations between the quality of the brain wiring and the electrophysiological activity in corresponding areas. However, the structural imaging method used in that study (diffusion tensor imaging) is not easily applied to the cerebral cortical structure. Therefore, we used estimated cortical thickness across the brain surface as the imaging phenotype in the last study. In Paper III we tested the hypothesis that cortical thickness in functionally relevant regions is sensitive to variability in specific attentional functions.

The attention systems of the brain enable the organism to filter, select and extract relevant information from a noisy and ambiguous environment. Attentional functions are fundamental for cognitive functioning, and are often compromised in psychiatric and neurodegenerative disorders contributing to cognitive impairment. Attention is far from a unitary construct or function, and might be defined and operationalized in many different ways. In the present study we used reaction time measures derived from a behavioral paradigm previously shown to correspond reasonably well with variability in brain activity patterns, including functional magnetic resonance imaging and electrophysiology, as well as genetic and lesion studies, namely the Attention Network Test (Fan et al., 2002; see below for further details).

The findings presented in Paper III supported the results from Paper I in suggesting a relatively close association between regional variability in brain structure and specific

cognitive functions, and thus provide clues as to which brain structures that might be involved in the impaired attentional functions often seen in disease and aging.

Summarized, while age-related changes in cognitive functions and brain macro- and microstructural anatomy show similar trajectories, the associations between them reflect the result of a complex interplay between a vast array of genetic, physiological and environmental processes. The present thesis aims at untangling some of these associations by utilizing advanced magnetic resonance imaging approaches; diffusion tensor imaging (DTI) and quantitative brain morphometry, in combination with electrophysiology and experimentally assessed attentional function. The overarching objective of the current project is to contribute to the ongoing work of bridging the gap between the cognitive and neurosciences in order to increase the knowledge about the aging mind in health and disease.

LIST OF PAPERS

I. Westlye LT, Walhovd KB, Bjørnerud A, Due-Tønnessen P, Fjell AM. (2009). Error-related negativity is mediated by fractional anisotropy in the posterior cingulate gyrus - a study combining diffusion tensor imaging and electrophysiology in healthy adults. *Cerebral Cortex, 19,* 293-304.

II. Westlye LT, Walhovd KB, Dale AM, Bjørnerud A, Due-Tønnessen P, Engvig A, Grydeland H, Tamnes CK, Østby Y, Fjell AM. (2010). Life-Span Changes of the Human Brain White Matter: Diffusion Tensor Imaging (DTI) and Volumetry. *Cerebral Cortex, 20*, 2055-2068.

III. Westlye LT, Grydeland H, Walhovd KB, Fjell AM. (2011). Associations between Regional Cortical Thickness and Attentional Networks as Measured by the Attention Network Test. *Cerebral Cortex, 21*, 345-356.

MAIN RESEARCH OBJECTIVES AND HYPOTHESES

PAPER I

The main objective of Paper I was to test the hypothesis of a relationship between the strength of the scalp recorded event-related potential (ERP) error-related negativity (ERN) (see below), which partly reflects the large-scale synchronization and integration of activity of distributed neuronal assemblies (Varela et al., 2001), and the microstructural properties of the underlying white matter in relevant areas as indexed by diffusion tensor imaging (DTI).

The ERN was chosen as the target ERP component in this study because it is known to be tightly related to complex cognitive processing, it is reliably identified in most participants, and the neuroanatomical sources are well described. In addition to the generator in the cingulate gyrus, evidence from several lesion studies suggests distributed cortical and subcortical involvement in the generation of the ERN. This indicates that the integrity of the white matter projecting to and from the cortical sources contribute to the component (Gehring & Knight, 2000; Hogan et al., 2006; Stemmer et al., 2004; Ullsperger & von Cramon, 2006).

Based on the putative association between white matter myelin and the fractional anisotropy index on one side (but see important limitations regarding this interpretation in the Methods section), and the importance of myelin for efficient and synchronous neuronal transmission, we hypothesized a positive correlation between the amplitude of the ERN and fractional anisotropy. We restricted the initial regional analysis to the cingulate gyri because these are assumed to serve as the main neuronal generators for the ERN.

PAPER II

Repeated demonstrations of nonlinear patterns of white matter volume changes through the lifespan have nurtured the hypothesis of protracted white matter maturation into middle age (Bartzokis, 2004). However, this putative prolonged maturation of the white compared to the gray matter has previously not been tested using DTI indices of white matter microstructural integrity. Since the human brain white matter develops slowly from infancy (Dubois, Dehaene-Lambertz, Perrin, et al., 2008; Giedd et al., 1999; Klingberg et al., 1999; Knickmeyer et al., 2008; Paus et al., 1999), an accurate modelling of the age-trajectories should be based on large samples including children, adults, and elderly participants. The

main objective of Paper II was to test the hypothesis of continued microstructural white matter maturation into middle adulthood by delineating regional lifespan trajectories of DTI indices of brain diffusivity and automatically estimated regional white matter volumes in 430 healthy participants aged 8–85 years. One of the main comparisons was made between the estimated maturational plateaus in various anatomical regions between DTI and volumetry, and we expected to see earlier peaks for the DTI indices compared to the tissue volumes.

Post-mortem studies of myelination in human infants have suggested a sequence of development with the earliest maturation seen in the central sulcus, including the cortico-spinal tract, and then a posterior-anterior gradient with earlier maturation in posterior compared with anterior areas (Kinney et al., 1988; Yakovlev & Lecours, 1967). Informed by previous neurodevelopmental DTI studies of children and adolescents (Lebel et al., 2008; Tamnes, Østby, Fjell, et al., 2010), we anticipated early developmental plateaus in motor and sensory pathways and a relatively protracted maturation of the frontotemporal circuitry. Lastly, as suggested by the notion of an inversed ontogenetic white matter degradation during the course of aging (Courchesne et al., 2000), we hypothesized early age-related changes in regions showing evidence of protracted maturation.

PAPER III

The attention systems of the brain help the organism to orient towards, select, filter and extract information from its often noisy and ambiguous surroundings. The efficiency of the attentional processes is therefore pivotal for cognitive functioning, and individual differences in attentional functions are likely related to variations in structural properties of the brain. Attention is not a unitary cognitive process, and models of the relationship between attentional functions and brain structure must take this into account. The Attention Network Test (ANT) (Fan et al., 2002) yields behavioral indices of three independent attentional components: executive control, alerting, and orienting. Executive control relates to the resolving of cognitive interference and conflict, alerting refers to the continuous maintenance of a vigilant (or alert) state, and orienting to the selection of and orienting towards sensory information in the environment.

Despite large interest in the ANT attentional components along several lines of investigations, it has not been known whether the ANT network scores correlate with macrostructural brain measures, e.g. cortical thickness, in relevant cortical regions. This is an important question pertaining both to the merits of the ANT as a cognitive phenotype in the

study of individual differences in healthy populations and to the neurocognitive sensitivity of a widely applied magnetic resonance imaging-derived morphometric measure. The main aim of Paper III was thus to delineate the relations between the three attentional subcomponents of the ANT and cortical thickness in a subsample comprising 263 healthy adults aged 20-85 years of age. Based on previous lesion, functional imaging and electrophysiological studies, we expected to see localized yet differentiated effects of each of the three attention networks.

Further, we sought to test two competing theories on brain-cognition associations. The first hypothesis might be referred to as the neurodevelopmental perspective, i.e. that maturational neurobiological perturbations determine the adult level of functioning. This theory suggests that the brain–behavior correlations should be relatively stable through the adult life span. An alternative hypothesis predicts that variability due to cortical atrophy in higher age is the main force driving the relationships in adult samples. This has been referred to as a neuropsychological perspective (Van Petten, 2004, see also Discussion section). In Paper III, we sought to investigate these two hypotheses by testing whether the observed associations between attention and thickness differed as a function of age, i.e. we modelled age by ANT interactions on cortical thickness, and also tested if the correlations between thickness and ANT scores differed between a young and old subsample.

RESEARCH QUESTIONS

PAPER I

Is the amplitude of the event-related potential error-related negativity associated with the microstructural integrity of the white matter in the cingulum bundle?

PAPER II

Are diffusion tensor imaging indices of microstructural integrity age-dependent, and if so, do they support volumetric evidence of a protracted maturation of the human brain white matter?

PAPER III

Is regional cortical thickness associated with specific attentional functions as measured by the Attention Network Test, and do these associations change as a function of age?

METHODS

DESIGN

Data presented in the current thesis is obtained from the first wave of the ongoing longitudinal research project *Cognition and Plasticity through the Life-Span* funded by the Research Council of Norway and coordinated from the Center for the Study of Human Cognition at the Department of Psychology, University of Oslo.

This is a methodologically multimodal project in the sense that we have utilized various different methods to shed light on the same underlying phenomenon. We have included several magnetic resonance imaging techniques, electrophysiology, standardized neuropsychological assessments and computerized experimental tests. The participants have been recruited through newspaper advertisements, and should thus be defined as a convenience sample.

Although longitudinal data will be available in the future, the present project utilizes a cross-sectional design. This implies that any interpretations of age-related *changes* in this thesis are in fact rather age-related *differences*. The limitations imposed by a cross-sectional design are well known, and includes cohort effects related to for example nutritional factors or available health care *in vitro* or during the course of early development, educational system, environmental toxins and so on. A cross-sectional design does not allow for statistical modelling of individual trajectories or rate of change. Although longitudinal designs also have serious limitations, including test re-test effects, non-random dropouts etc, interpretations from the presented data should be made with caution and should be replicated and supported with longitudinal data.

PARTICIPANTS

The data material presented in Papers I-III consisted of highly overlapping samples of participants. The sample used in Paper I (n = 100) and Paper III (n = 263) was drawn from the first wave of *Cognition and Plasticity through the Life-Span*. In Paper II we combined data from the same project (20-85 years) and the parallel neurodevelopment project *Neurocognitive Development* (8-19 years) in order to obtain a lifespan sample comprising 430 subjects in total. The *Neurocognitive Development* project is also funded by the Norwegian Research Council and coordinated from the Center for the Study of Human Cognition at the

Department of Psychology, University of Oslo. Imaging parameters were kept identical in these projects to facilitate comparisons across a wide age span.

All participants were recruited through newspaper ads or among students and employees at the University of Oslo. Written informed consent was obtained from all participants above 12 years of age, and from parents of the participants of 12 years of age or younger. Demographic details for all included subjects per decade and in total, including sex distribution, education, general intellectual abilities, Mini Mental Status and age are summarized in Table 1 in Paper II.

All subjects were right-handed native Norwegian speakers. We employed several screening procedures to minimize the possible influence of early or incipient neurodegeneration. Participants were not subjected to a full medical assessment but were screened using a standardized health interview per telephone prior to inclusion in the study. Participants with a history of self- or parent-reported neurological or psychiatric conditions including clinically significant stroke, serious head injury, untreated hypertension, diabetes, and use of psychoactive drugs within the last 2 years were excluded. Further, participants reporting worries concerning their cognitive status, including memory function, were excluded. Further, we used standardized screening instruments to exclude subjects with signs of depression (Beck Depression Inventory; Beck & Steer, 1987)) and cognitive decline (Mini Mental State Examination; Folstein et al., 1975). All participants above 20 years of age scored < 16 on Beck Depression Inventory and subjects above 40 years of age scored ≥ 26 on Mini Mental State Examination. General cognitive abilities were assessed by Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), and all subjects scored within normal Intelligence Quotient range (82-145).

Most participants were assessed at three different occasions no more than 3-4 months apart. The usual order of assessments was as follows: Day one consisted of screening and neuropsychological and cognitive testing, day two of the recordings of electroencephalography while performing computerized tasks and day three consisted of MRI scanning. All participants were reasonably compensated for their time, transport, etc.

COGNITIVE ASSESSMENTS

All participants in the present study have been assessed using validated and standardized neuropsychological and computer-based tests designed to measure specific cognitive functions. In the present thesis, data from a subset of the tests have been analysed

and presented, with a particular focus on computerized tasks demanding efficient attention and speed. The tasks were chosen because they have previously been suggested as valid cognitive phenotypes. All participants were screened for depression using the Beck Depression Inventory (Beck & Steer, 1987) to minimize possible confounding effects of depressive symptoms on cognitive functioning. Further, all participants above 40 years of age were screened for cognitive decline related to possible neurodegenerative disease using the Mini Mental State Examination (Folstein et al., 1975). See above for a more detailed summary of the screening procedures and exclusion criteria employed. In Papers I-III, we report measures of general cognitive abilities as assessed by the four subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; matrices, block design, vocabulary and similarities) (Wechsler, 1999). These data are mainly reported as background variables describing the general intellectual functioning of the sample.

In Paper I and Paper III, respectively, we present brain structural correlates of two widely used behavioral paradigms assumed to tap various forms of attentional and cognitive control mechanisms, namely the Eriksen Flanker Task (Eriksen & Eriksen, 1974) and the Attention Network Test (Fan et al., 2002).

Eriksen Flanker Task

In Paper I, we administered a modified version of the classic Flanker task (Eriksen & Eriksen, 1974), which is a speeded response task. Different versions of the task have been used to measure aspects of attention, cognitive control and error processing. The stimuli used in the present version were horizontal arrowheads of length 1 cm (approx 1°), pointing either to the right or the left displayed in a vertical stack 2.5° high. Subjects were instructed to respond as accurately and quickly as possible by button presses indicating which direction the middle arrow was pointing. Each trial consisted of the following stimuli; first, a fixation cross was presented for a random interval ranging between 1200 and 1800 ms. Then the four flanker arrows were presented for 80 ms before the target arrow was presented for 30 ms along with the flanker arrows. At presentation of the target arrows, the task was to push one button if the target was pointing to the left and another button if the target was pointing to the right. Based on the mean reaction time for the 20 first trials, an individually adjusted reaction time criterion was set. After every subsequent third trial with reaction time exceeding this criterion, a message occurred on the screen for one second instructing the participant to

respond faster. This was implemented to increase the demand to respond swiftly and thus increase task difficulty.

Responses were obtained on a Psychology Software Tools Serial Response Box, and the experimental procedures and responses were collected using E-prime (Psychology Software Tools, Pittsburgh, PA). There were two task conditions; congruent and incongruent. In the congruent condition all arrows were pointing in the same direction. In the incongruent condition, the middle arrow was pointing toward the opposite side as the flanker arrows. The task included 416 trials with a short break halfway. The probability of an incongruent trial was 50 % with a rule of no more than three consecutive incongruent trials. A schematic of the Flanker task employed in Paper I is shown in Figure 2.

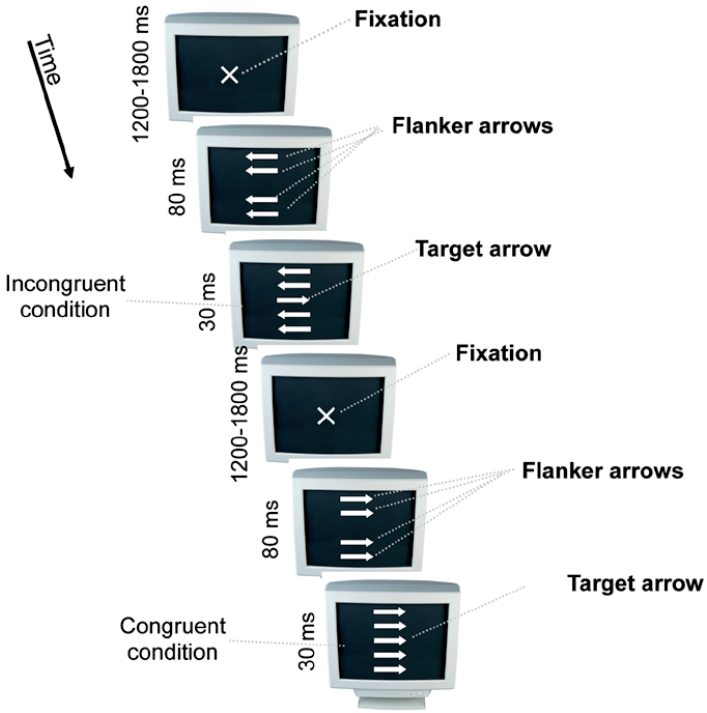

FIGURE 2: A schematic representation of the Eriksen Flanker Task. The size of the fixation cross and arrowheads have been increased for visualization purposes. Adapted from Paper I (Westlye, Walhovd, Bjørnerud, et al., 2009).

The Flanker task and similar behavioral paradigms have been shown to yield a reliable number of commission errors in the incongruent condition (Debener et al., 2005), and also to produce the well described congruence effect on reaction time with slower reaction time in the incongruent compared with the congruent condition (Eriksen & Eriksen, 1974). The congruence effect is partly reflecting response conflict induced in the incongruent condition by the incompatible target arrowheads (Botvinick et al., 2001). In Paper I, we were interested in the immediate electrophysiological potential after erroneous responses. To exclude possible condition and conflict related interactions with the measured potentials (van Veen & Carter, 2002), we focused on data from the incongruent condition only. To exclude participants with suboptimal motivation, we employed three behavioral exclusion criteria. First, no participants with less than 80 % accuracy in congruent trials were included. Second, participants with a non-significant congruence effect on reaction time in correct trials were excluded. The third criterion employed was number of accepted incongruent commission error ERP trials, and participants with less than 10 trials were excluded. However, subjects with less than 15 error trials were only accepted upon manual inspection of the average ERP curves. 13 participants were excluded on the basis of these three criteria, and the analysis reported in Paper I is based on the remaining 87 participants.

The Attention Network Test

In Paper III, we used behavioral data from the Attention Network Test (ANT). ANT is a widely used experimental task that combines the cued reaction time (RT) task (Posner, 1980) and the Eriksen flanker task (Eriksen & Eriksen, 1974) into one experimental paradigm effectively parsing three largely independent attentional components: executive control, alerting, and orienting (Fan et al., 2009). Briefly, executive control pertains to the processing and resolving of cognitively incongruent or conflicting stimuli, the alerting component to the achievement and maintenance of a vigilant state, and orienting to the selection of and orienting toward sensory information (Posner, 2008; Posner & Petersen, 1990). Although still a matter of some controversies (Callejas et al., 2005; Callejas et al., 2004), evidence from both genetic (Fan et al., 2003; Fossella et al., 2008; Fossella et al., 2002), pharmacological (Brunye et al., 2010), electrophysiological (Fan et al., 2007; Neuhaus et al., 2010), functional neuroimaging (Fan et al., 2005; Thiel et al., 2004), diffusion tensor imaging (Niogi et al.,

2010), and behavioral (Fan et al., 2002) studies support the relative independence of the different attentional components derived from the ANT.

Functional neuroimaging studies have shown that the different attentional components are subserved by anatomically separate cortical networks (Fan et al., 2005). Executive control has been shown to invoke cortical neurocircuitry known to be recruited during various cognitive control tasks, including the anterior cingulate, lateral prefrontal cortices, and the right inferior frontal gyrus (Aron et al., 2004; Bush et al., 2000; Fan et al., 2005; MacDonald et al., 2000), and is largely influenced by the ventral tegmental dopamine system (Brocki et al., 2009). Alerting has been associated with frontoparietal cortical networks, especially in the right hemisphere, and the thalamus, and is assumed to be modulated by the cerebral distribution and availability of noradrenaline (Beane & Marrocco, 2004). Finally, the orienting component, which is manipulated by the presentation of a cue indicating the spatial localization of attention, has been related to both superior parietal (Corbetta et al., 2000) and superior frontal (Fan et al., 2005) areas and has been linked to the workings of the acetylcholine system (Davidson & Marrocco, 2000). Figure 3 shows a schematic representation of the brain neurocircuitry involved in the various attentional components.

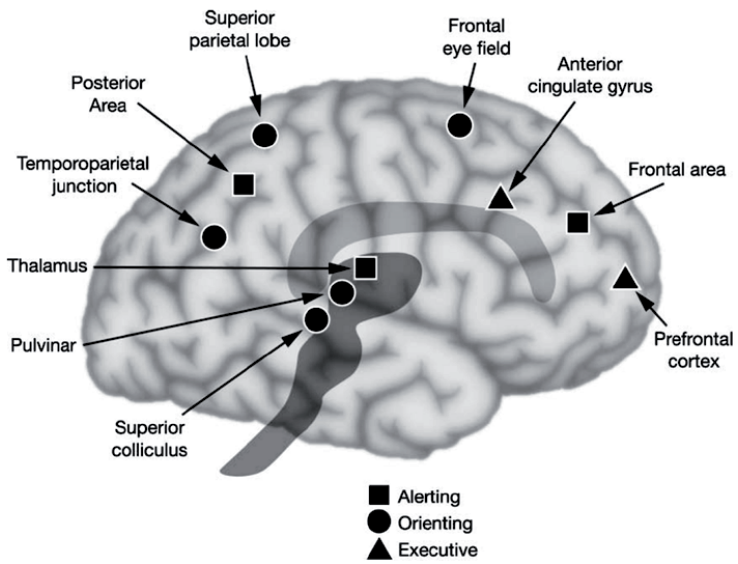

FIGURE 3: The neuroanatomy of attention. Adapted from Posner & Rothbart (2007).

ANT has been used to untangle attentional deficits in several clinical disorders, including attention deficit hyperactivity disorder (Johnson et al., 2008; Konrad et al., 2006), schizophrenia (Nestor et al., 2007; Wang et al., 2005), and Alzheimer's disease (Fernandez-Duque & Black, 2006). Furthermore, the task has revealed beneficial effects of bilingualism on the executive and alerting systems (Costa et al., 2008). The task has also been used to delineate normal cognitive development during childhood (Rueda et al., 2004) and attentional alterations during cognitive aging (Fernandez-Duque & Black, 2006; Jennings et al., 2007). Collectively, evidence from various lines of investigations, including clinical, genetic, neuroimaging and electrophysiological approaches, suggest that ANT is an efficient, valid and reliable test for parsing independent attentional systems based on reaction time data. ANT is based on psychological theory, validated using imaging techniques and used to investigate gene–brain–behavior associations. ANT thus provides a promising theoretical and empirical framework in the search of associations between brain and cognition. Figure 4 presents a synopsis of functional neuroimaging, neurotransmitter and genetic evidence validating the independence of the attentional networks.

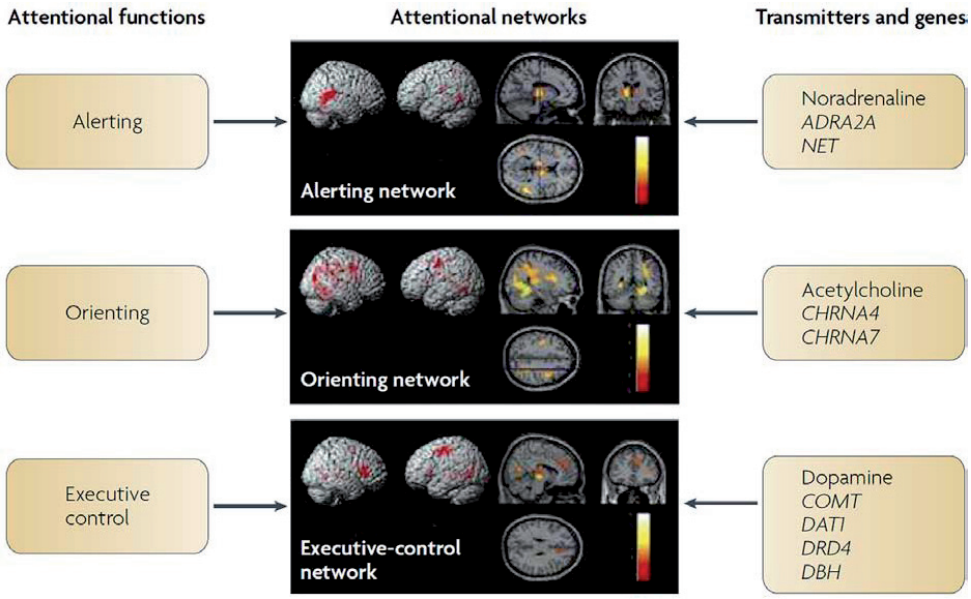

FIGURE 4: Functional correlates and putative relevant neuromodulators and genetic mediators of the attention networks. Adapted from Green et al. (2008).

Despite the vast interest in the ANT along several lines of investigations, it has not been known whether ANT subcomponents correlate with macrostructural brain measures, e.g. cortical thickness, in relevant cerebral regions. This is an important question pertaining both to the merits of the ANT as a cognitive phenotype in the study of individual differences in healthy populations and to the neurocognitive sensitivity and specificity of a widely applied magnetic resonance imaging-derived morphometric measure.

The main aim of Paper III was thus to delineate the relations between the three attentional subcomponent of ANT in a large sample comprising 263 healthy adults of 20-85 years of age. We administered a version of the ANT (Fan et al., 2002) downloaded from Dr. Jin Fan's website (http://www.sacklerinstitute.org/users/jin.fan/). This version consisted of two runs of 96 trials preceded by one practice run with 20 trials. During assessment, participants were seated in a chair at approximately 60 cm distance from a 19-inch computer monitor. For each trial, the participants pressed a key indicating whether a target arrowhead was pointing to the left or right. The arrowhead was presented either above or below a centrally located fixation cross. The target was flankered by one of three different types of stimuli; 1) pairs of congruent arrows, 2) pairs of incongruent arrows, or 3) pairs of neutral lines. Each type of flanker stimuli was presented 32 times per run. Furthermore, each trial was preceded by one of four cue conditions, with each variant occurring 24 times in each run: 1) no cue, 2) center cue, 3) double cue, and 4) spatial cue. The cues, when presented, were single (center and spatial cue condition) or double asterisks replacing (center cue) or accompanying the fixation cross. The size of the fixation cross was approximately 0.5 × 0.5 cm (~0.5°), and the diameter of the asterisks used for cuing was about 0.3 cm (~0.3°). Target arrows (or dashes in the neutral condition) were centered 1.3 cm (~1.2°) below or above the fixation cross. Each trial was initiated by the fixation cross of variable duration, equally distributed across cuing and flanker conditions. The fixation cross was followed by the cue condition of 100 ms duration and then the target stimuli, which remained visible on the screen until response or until 1700 ms after target presentation. The participants were instructed to emphasize speed and accuracy throughout the session. Responses were obtained on a Psychology Software Tools Serial Response Box, and the experimental procedures and responses were collected using E-prime (Psychology Software Tools, Pittsburgh, PA). See Figure 5 for an overview of the task.

One of the main features of the ANT is the feasibility to extract specific attentional components based on reaction time in the various cue and target conditions. Based on previous literature, we defined the executive control network as the difference in reaction time

between the incongruent and the congruent condition, alerting as the difference in reaction time between the no cue and the center cue condition, and orienting as the difference in reaction time between the center cue and the spatial cue condition. Since overall reaction time increases substantially with advancing age, we adjusted the component scores with the relevant baseline reaction time in order to isolate the attentional system from the anticipated increase in overall response time, i.e. age-related global slowing.

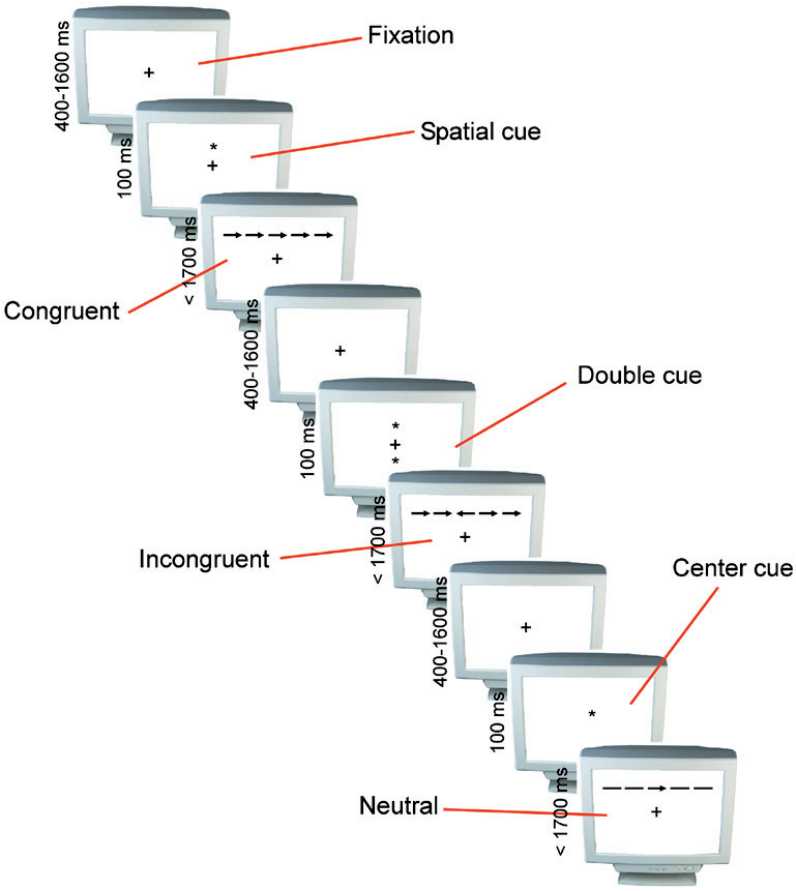

FIGURE 5: Schematic of the Attention Network Test. The size of the fixation cross, warning cues and target arrowheads are increased for visualization purposes. Not shown: Warning cues were followed by a blank screen of 400 ms duration prior to the presentation of the targets.

NEUROIMAGING

The generation of the profoundly detailed images of body organs made available by magnetic resonance imaging is a complex process of which the details lies beyond the scope of this thesis. Briefly, magnetic resonance imaging is based on the absorption and emission of electromagnetic energy in the radio frequency range, and usually relies on the spinning motion of the hydrogen nucleus present in the water molecules in biological tissue. These nuclei align their rotational axis according to the magnetic field applied. The head of the subject (or any other organ) is placed in a static magnetic field within the bore of the scanner. This aligns the magnetic moments of the protons in a parallel or anti-parallel fashion relative to the magnetic field. Next, the steady state is transiently perturbed by radio frequency pulses, which bring the proton spins into a higher energy state. The absorbed energy is subsequently released with a tissue specific time constant and can be recorded as an oscillating electromagnetic field by a detector (coil) placed over the head of the subject. By applying additional magnetic fields which vary as a function of position, information about the spatial origin of the detected signals can be obtained and reconstructed into detailed MR images of the organ.

Magnetic resonance imaging is a completely non-invasive imaging technique, and has proven extremely useful both in clinical and research settings. One of the main advances of magnetic resonance imaging in a neuroscience research setting is the high level of detail obtained in the images along with the high soft tissue contrast which makes it possible to separate different tissue classes in the human brain based on the signal intensity. Varying the imaging parameters and contrasts applied during data collection enables quantification of several biological properties.

Diffusion tensor imaging

One such property is diffusion, which reflects the random movement of water within the tissue. Diffusion MRI is able to measure the displacement of water molecules in the 5-10 μm range over time spans of tens of milliseconds. The distance travelled by the water molecules depends on its interactions during that time. Therefore, careful analysis of the degree and pattern of the water displacement enables structural inferences at the microscopic level. Diffusion tensor imaging is a technique in which the motion of water molecules is estimated in different spatial directions in the three dimensional space. The signal intensities at each voxel in the volume are attenuated, depending on the strength and direction of the

diffusion gradient and the local microstructure in which the water molecules diffuse. Stronger attenuation in the image at a given position indicates greater diffusion in the direction of the diffusion gradient. To increase the precision of the brain tissue's diffusion profile, one need to repeat the scans, applying different directions of the diffusion gradient for each scan. The measures (signal attenuations) in every volume element (voxel, which is a three dimensional pixel) in the MR volume are fitted to a tensor model ("ellipsoid"). Six parameters are necessary to describe the tensor, namely the three eigenvectors that define the orientations in three dimensional space and the three eigenvalues which denote the length of each corresponding vector. While six spatially independent measures are sufficient to mathematically describe the tensor, degree of diffusion is usually estimated along a higher number of independent directions in order to increase the reliability and precision of the estimated tensor. See Figure 6 for a schematic representation of the diffusion tensor and a visualization of the directions used in the present project. Here, diffusion was measured along 30 independent directions in the three dimensional space. Please see Paper I and Paper II for more details regarding the pulse sequence used.

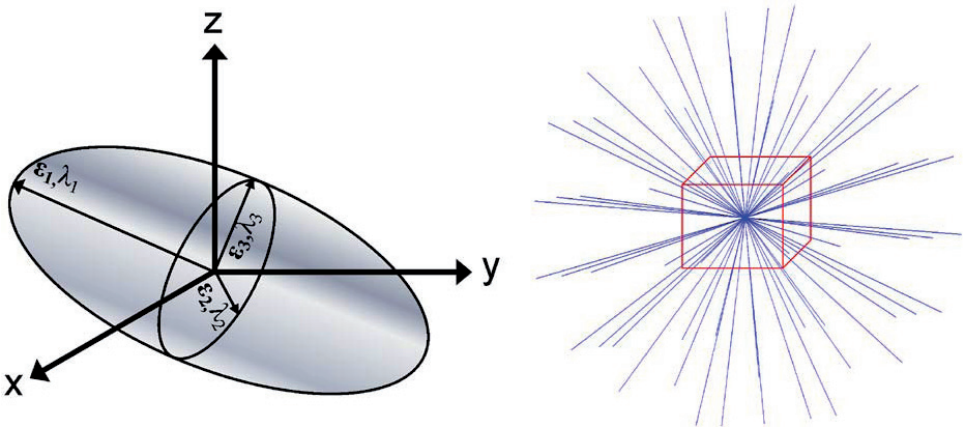

FIGURE 6: Left: The diffusion tensor (the ellipsoid) with its eigenvectors (ε_1, ε_2, ε_3) which describe the direction in the three dimensional space and corresponding eigenvalues (λ_1, λ_2, λ_3) which describe the length of each vector. Right: A 3D plot of the diffusion vector matrix used in the present thesis. Diffusion is measured along every direction in the three dimensional space in each voxel in the MRI volume.

Importantly, the shape of the diffusion tensor is related to the cytoarchitecture of the underlying tissue. The largest eigenvalue (λ_1) is assumed to represent the apparent diffusion of water along the length of the axonal fiber. The two smaller eigenvalues (λ_2, λ_3) are assumed to reflect the diffusion across (perpendicular) the fiber. The two smallest eigenvalues might be averaged to yield a single value, often termed radial diffusivity (RD).

A characteristic feature of the motion of water in biological tissue is that it is restricted, yielding an anisotropic diffusion pattern. This means that the degree of diffusion is larger in one compared to at least one of the two other directions, i.e. that the three eigenvectors are not of equal length. The degree of anisotropy can be calculated from divergences between parallel and perpendicular diffusion. One popular index in brain imaging studies is fractional anisotropy (FA), which is the normalized standard deviation of the eigenvalues in the diffusion tensor (Pierpaoli et al., 1996). Another popular measure is the mean diffusivity (MD), which is the mean of all three eigenvalues, and thus represents the bulk diffusivity in the voxel ignoring directional preferences.

Diffusion of water molecules in biological tissue is restricted by axonal membranes, microtubules and myelin sheaths, and DTI is sensitive to the direction and degree of water displacement (Beaulieu, 2002; Le Bihan, 2003). Since water diffuses more rapidly along (parallel) than across (perpendicular) the axon, DTI enables detailed images and quantitative measures of the fiber bundles wiring the cerebral neurocircuitry (Mori & Zhang, 2006). Recent advances in analysis techniques have fuelled an explosive interest in disconnection models proposing that structural connectivity modulates the functional and cognitive impairments in aging and various disorders (Chanraud et al., 2010).

The merit of DTI as a useful imaging phenotype is dependent of it sensitivity to biologically relevant information. The causes of anisotropic diffusion in human brain tissue are not fully understood, but axonal membranes are shown to be the primary determinant of diffusion anisotropy of water in neural fibers, while myelin can modulate the degree of anisotropy in a given tract (Beaulieu, 2002). Although non-specific, DTI is a putative imaging phenotype for myelin-related processes in the brain. The human brain shows significant alterations in the myelin architecture during the course of aging (Peters, 2002), and it is believed that such alterations are related to the cognitive alterations seen in both aging and neurodegenerative disease (Bartzokis, 2004). Thus, DTI might prove to be a highly informative and valuable imaging technique in the study of the aging human brain.

There are several ways of performing cross-subject statistical analysis on DTI data. In order to achieve comparison of diffusion parameters between subjects, it is first necessary to

solve the correspondence problem, which refers to the challenges related to performing cross-subject statistical analysis on brains with different size, sulcal and gyral curvature, geometry, etc. Although not an optimal solution, these concerns are typically alleviated by transforming all individual images into some common space or coordinate system and then applying a certain degree of blurring/smoothing of the images. In the present thesis, we have utilised a combination of tract-based spatial statistics (TBSS) (Smith et al., 2006; 2007) and regions-of-interest (ROI) based measures using digitalized probabilistic neuroanatomical white matter atlases (Hua et al., 2008; Mori et al., 2005; Wakana et al., 2004). TBSS aims to solve the alignment issue by estimating a group mean FA skeleton, which represents the centers of all fiber bundles that are common across the subjects involved in a study. Individual FA data are projected onto the mean FA skeleton in such a way that each skeleton voxel takes the FA value from the local center of the nearest relevant tract, thus minimising issues of alignment and correspondence.

Briefly, TBSS involves the following steps: 1) Alignment of all subjects' FA images to a common target using non-linear registration. 2) Creation of an average of all aligned FA images and thinning to create a skeletonized mean FA image. This image is thresholded to exclude areas of low mean FA or high cross-subject variability. 3) Projection of each subject's aligned FA volume onto the skeleton, by filling the skeleton with FA values from the nearest relevant tract center. This is achieved, for each skeleton voxel, by searching perpendicular to the local skeleton structure for the maximum value in a given subject's FA image. 4) Carry out voxelwise statistics across subjects on the skeleton-space FA data. See Smith et al. (2006; 2007) for more details. Figure 7 shows the output from various steps in the DTI data processing scheme employed in the present thesis and Figure 8 select neuroanatomical tracts of interest.

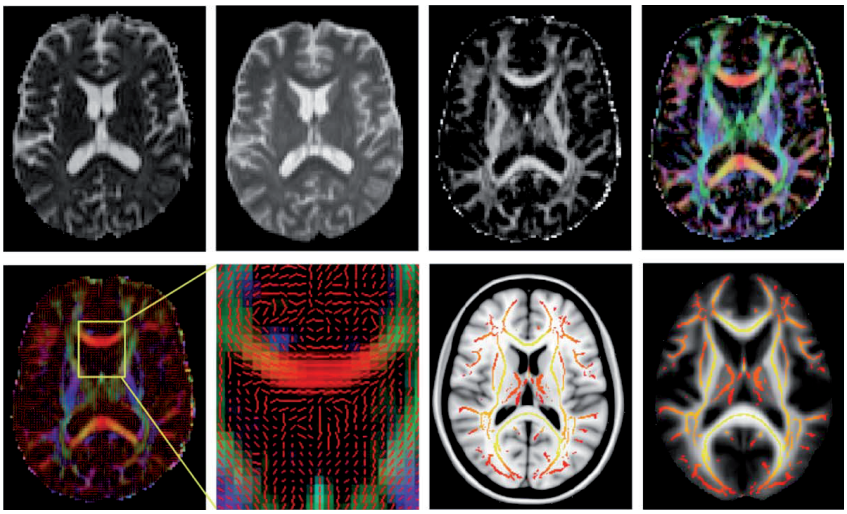

FIGURE 7: Sample images from the DTI processing scheme. Top, left: non-diffusion weighted volume (b=0), mean diffusivity, fractional anisotropy, color-coded vector volume (red: commisures, green: association tracts, blue: pyramidal tracts). Bottom, left: line-coded vector map, lines follow the fibers in the genu of the corpus callosum, the skeleton generated by TBSS superimposed on a standard brain and the skeleton superimposed on a mean FA map. Adapted from Westlye et al. (2008).

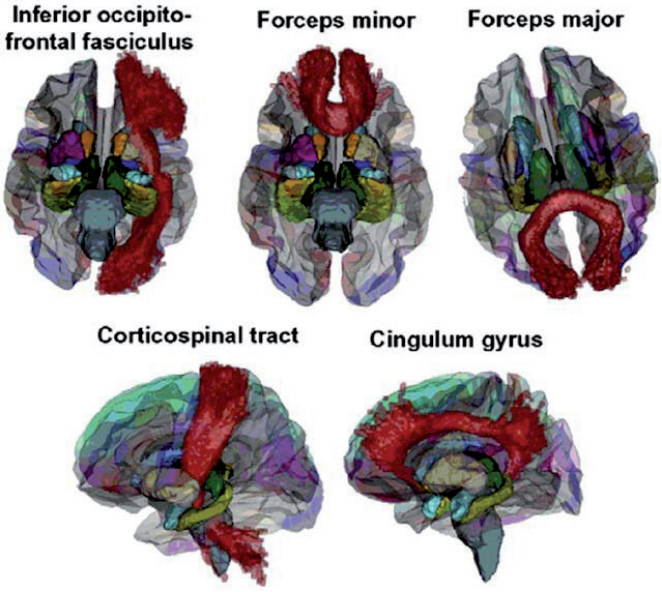

FIGURE 8: Selected three dimensional tracts of interest (red areas) visualised in the context of a semi-transparent standard brain and its volumetric segmentation.

Cortical thickness and volumetry

In addition to the diffusion weighted magnetic resonance imaging, we report data from T1-weighted data in Paper II and Paper III. The T1-weighted images are high-resolution anatomical scans. Please see Paper II and Paper III for details regarding the pulse sequence used. In the present thesis, we have used FreeSurfer for automatic tissue segmentation, cortical thickness estimation and tissue volume calculations. We estimated vertex-wise cortical thickness across the brain surface by means of an automated surface reconstruction scheme described in detail elsewhere (Dale et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl et al., 2001; Fischl, Sereno & Dale, 1999; Fischl, Sereno, Tootell, et al., 1999). Thickness measurements are obtained by reconstructing representations of the gray/white boundary and the cortical surface and then calculating the distance between the surfaces at each vertex across the mantle (see Figure 9). This procedure is capable of detecting submillimeter differences between groups, yielding a highly sensitive morphometric measure.

Next, the cortical surface is automatically parcellated into neuroanatomical regions based on a surface-based atlas, local curvature information and contextual information, yielding 33 surface-based regions in each hemisphere (Desikan et al., 2006; Fischl et al., 2004). The regional WM volume measures analysed in Paper III were estimated by labelling white matter voxels within a distance of 5 mm from the cortical surface according to the neuroanatomical label of the nearest cortical point (Salat et al., 2009) yielding 33 bilateral gyral WM segmentations (see Figure 10). Thus, each individual's T1-weighted MRI volume is automatically segmented into cortical gray and subcortical white matter parcels, enabling precise cortical gray matter thickness and subcortical white matter volume estimations in individually adjusted neuroanatomical labels.

In order to perform point-by-point analysis on cortical thickness, the individual maps are resampled, mapped to a common surface, smoothed, and submitted to statistical analyses. The surface-based mapping from native to standard space involves a nonrigid high-dimensional spherical averaging method to align cortical folding patterns (Fischl, Sereno, Tootell, et al., 1999). This provides accurate matching of morphologically homologous cortical locations on the basis of each individual's anatomy, enabling statistical analysis on a vertex by vertex basis while maintaining a high degree of spatial correspondence between invididuals.

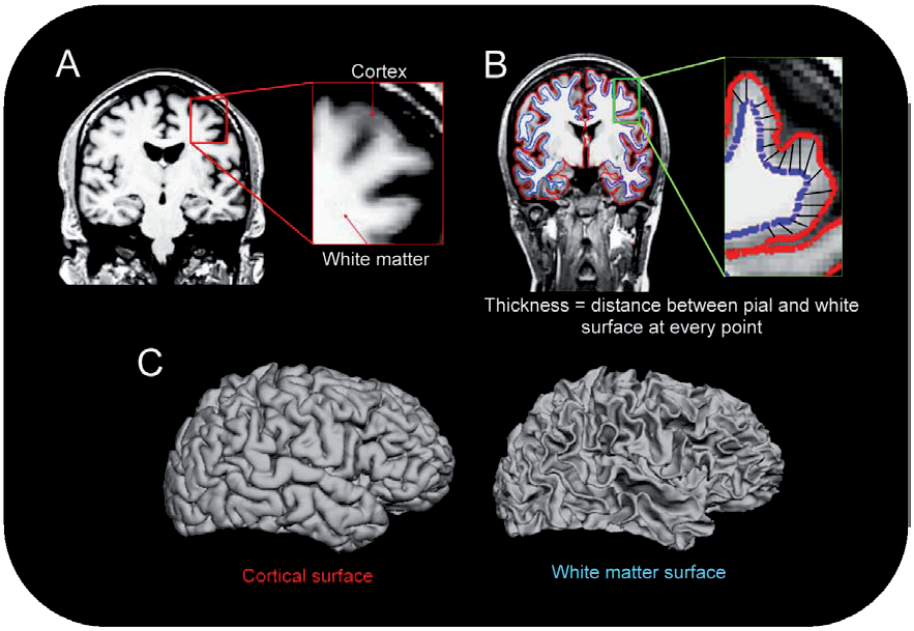

FIGURE 9: The surface reconstruction scheme employed in FreeSurfer. A) A coronal section of a T1-weighted MRI volume. The magnified part shows the contrast in signal intensity between the cortical gray and subcortical white matter. B) Automatic reconstruction of the boundaries between gray and white matter (blue) and between gray matter and cerebrospinal fluid (red). Cortical thickness is defined as the distance between the blue and the red line at every point across the cortical mantle. C) A three dimensional representation of the cortical (left) and white matter (right) surfaces.

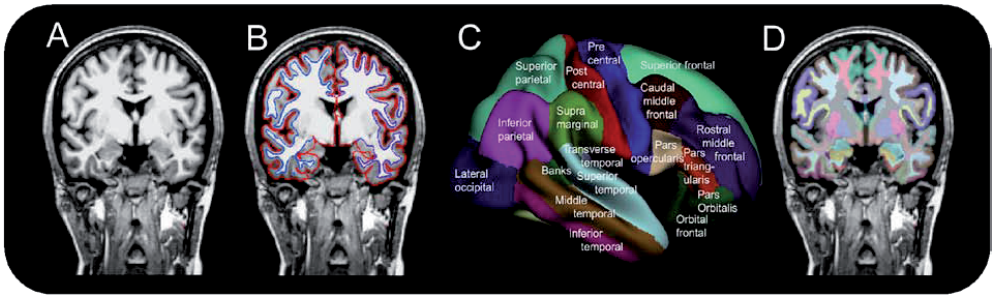

FIGURE 10: Neuroanatomical parcellation of the brain surface. A) A coronal section of a T1-weighted MRI volume. B) Automatic reconstruction of the boundaries between gray and white matter and between gray matter (blue) and cerebrospinal fluid (red). C) The result of the automatic surface-based parcellations scheme. D) T1-weighted MRI volume automatically segmented into neuroanatomical cortical and subcortical regions.

Event-related potentials

Event-related potentials (ERPs) are calculated based on segments of the continuous electroenecephalogram (EEG) recorded during e.g. task performance. The voltage patterns along the time scale comprising an ERP reflect the fundamental processing of sensory information and cognitive processes including e.g. selective attention, updating of memory, semantic decoding and comprehension, and performance monitoring. An ERP is locked to a certain physical or psychological/cognitive event, for example a stimulus presentation or a response, and are usually extracted from the EEG by means of averaging across several corresponding trials. An ERP component might be defined by its polarity (negative or positive relative to a reference channel), its spatial distribution on the scalp, its latency relative to the start of the event, and its relation to experimental variables (Luck, 2005).

Although the neurophysiological foundation for the scalp-recorded EEG is not completely understood, it is assumed that it, at least partly, reflect rhythmic, or oscillatory, synchronised waves of excitatory synaptic potentials of the thalamocortical system (Luck, 2005). The EEG reflects the electrical changes in large groups of neurons rather than single neurons, and is the result of various electrical sources in many small zones of the cortical surface beneath the electrode. The EEG does probably not reflect action potentials *per se*, but rather alterations in membrane potentials, i.e. inhibitory and excitatory post-synaptic potentials and de- or hyperpolarization of large neuronal assemblies (Varela et al., 2001).

There are many sources of noise influencing the scalp EEG, including the invariant orientation of cortical neurons relative to the scalp which causes the signals in some groups of neurons to cancel. Another important limitation is the inverse problem, i.e. that the relation between the EEG recorded on the scalp and the cortical neuronal sources is far from simple. Inferring the spatial pattern of neuronal activity based on the scalp recorded EEG is thus a challenging task. Further, the averaging procedures employed in conventional ERP studies does not enable a full analysis of the spatiotemporal dynamics of the ongoing EEG (Makeig et al., 2004). However, ERPs still yield functional correlates of cognitive processes in the normal human brain with a superb temporal resolution compared to functional imaging techniques based on magnetic resonance imaging. The time courses and latencies of ERP components track the dynamics of the processing activity in milliseconds (1/1000 s), whereas their amplitudes indicate the extent of neural resources allocation to specific cognitive processes (Duncan et al., 2009). Variation in the patterns of the components between individuals or groups of individuals therefore enables inferences about the variation in brain function.

In Paper I, EEG recordings were performed with a 128 Channel EasyCap Montage No. 15 with a sampling rate of 1000 Hz. This means that we recorded 1000 measurements per second concurrently from 128 electrodes mounted on the subject's scalp. The scalp signals were amplified with Neuroscan SynAmps2 and filtered online with a 30-Hz low-pass and 0.15-Hz high-pass analog filter prior to digitalizing and saving of the continuous data set. All electrodes were referenced to a common electrode placed on the left mastoid. Figure 11 shows a schematic of the channel setup and sample EEG data from four channels as well as a typical ERP. Vertical eye blinks were recorded from bipolar electrodes above and below the left canthi and impedances were kept below 10 kOhm. During recordings, participants were seated in a shielded Faraday chamber in a comfortable chair at about 60 cm distance from a 19-inch computer monitor while performing the Flanker Task.

The processing of the continuous EEG data included segmenting the data into epochs of 1000 ms duration, starting 600 ms prior to response and lasting until 400 ms after response. The epochs were linearly detrended in order to remove drift, and baseline corrected relative to a 100-ms time window –600 to –500 ms prior to response. Epochs containing signals ±100 μV were excluded. The epochs were corrected for eye blinks (Semlitsch et al., 1986) and digitally filtered with a 30-Hz low-pass filter. Remaining epochs containing response locked correct and erroneous responses from incongruent trials were extracted for further analysis.

Trials from erroneous and correct trials were averaged separately for each subject. Grand average curves and topographical plots for error trials revealed a maximum peak on a frontocentral channel, corresponding to previous literature (Taylor et al., 2007). A principal component analysis with peak amplitude from 22 selected electrodes yielded four clusters. One cluster comprising frontocentral channels explained 51.7 % of the variance in the measured activity, representing a valid candidate for the ERN. To minimize single electrode noise and signal distortions, the mean of three channels were chosen to represent the ERN in further analyses.

The grand average ERN and the corresponding topographic distribution are shown in Figure 12. Peak amplitude is influenced by high frequency signals, and might therefore not be an accurate estimate (Luck, 2005). Therefore, individually adjusted average amplitudes were estimated by averaging the measured potential in the 20 ms preceding and 20 ms after peak amplitude for each participant. These individually computed peak amplitudes were submitted to statistical analysis in order to explore the associations between amplitude, diffusion tensor imaging and behavioral measures obtained from the Flanker task.

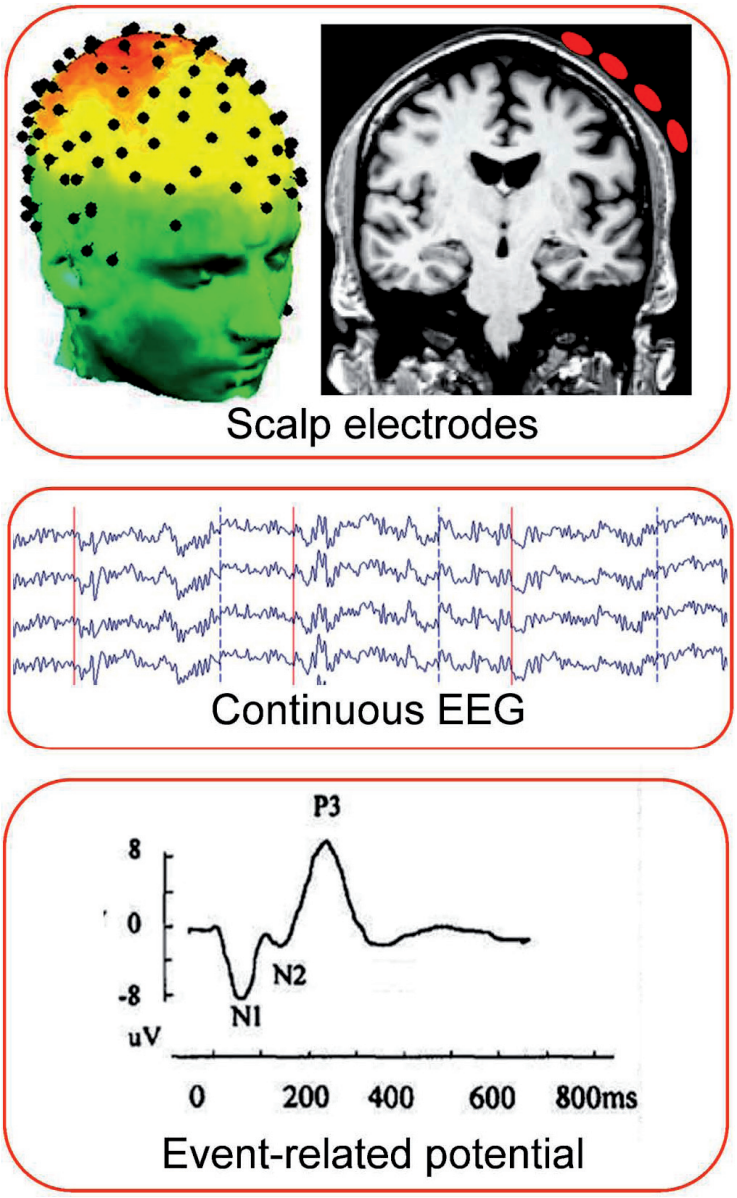

FIGURE 11: Upper, left: Three dimensional head plot showing the electrode scheme used in Paper I. Right: A schematic visualization of the scalp electrodes and the underlying brain. Middle: Three seconds of segmented EEG data from four different scalp electrodes. The vertical lines denote the start of a new segment/epoch (blue) and responses (red), respectively. Bottom: A typical ERP exhibiting the characteristic early components N1 and N2 as well as the later P300 complex. The ERP is an average of several segments from the continuously recorded EEG.

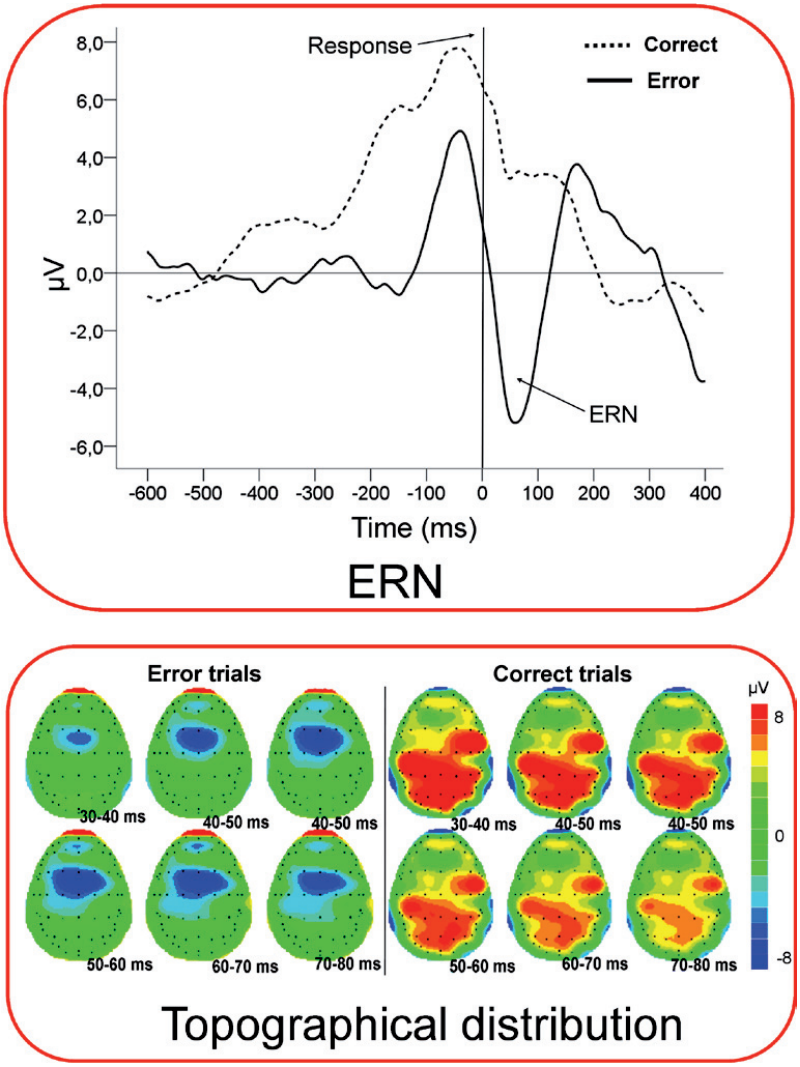

FIGURE 12: Upper row: The grand average ERP across all subjects after correct (dashed line) and erroneous (solid line) responses. The ERN is clearly seen as a negative deflection following error responses, peaking approximately 60 ms after response. Bottom row: the topographical distribution of the signal at different time points after erroneous (left) and correct (left) responses. The ERN is characterized by a sharp negativity localized in frontocentral parts of the scalp, likely reflecting anterior cingulate activity in response to errors.

STATISTICAL ANALYSIS

Although the statistical procedures used in Paper I-III have several aspects in common, they will be presented independently for clarity. If not explicitly stated otherwise, the statistical procedures have been performed using SPSS for Windows, Release Version 16.0 (© SPSS, Inc., Chicago, IL).

Paper I

For analysis of DTI data the randomise tool within FSL (Smith et al., 2004; Woolrich et al., 2009) was used to carry out permutation-based (Nichols & Holmes, 2002) cluster inference (Worsley, 2001) within *a priori* defined regions of interest. To test for regional nonspecific associations between FA and ERN, a linear regression with mean FA in the skeleton and ERN amplitude was performed. To test for local correlations and anatomical specificity, a general linear model (GLM) of the effect of ERN amplitude on FA was fitted in every voxel included in the skeleton, and the number of significant voxels ($p < .05$, uncorrected) within different probabilistically defined fiber tracts were counted.

Statistical clusters were defined by thresholding the raw t-statistics map of the TBSS skeleton at $t > 2.5$, and then searching for contiguous clusters of suprathreshold voxels. The null distribution of the cluster size statistic was produced by 5000 random permutations of the effect of ERN on FA, recording the maximum cluster size across space at every permutation. The null distribution should thus be considered empirical as opposed to parametric with a predefined statistical distribution (e.g. t or F distribution). Clusters were then thresholded at $p < .05$, yielding cluster probability maps fully corrected for multiple comparisons across space. Age and sex were allowed to covary in the models in order to control for possible confounding age or sex related effects.

Mean FA within significant clusters was calculated for each participant, fed to a linear regression analysis and plotted against ERN amplitude to visualize the association between FA and ERN. Next, we tested the relationship between ERN and the principal and radial diffusivity, respectively. This was done to further explore the neurobiological underpinnings of the effects of ERN amplitude on DTI. This was achieved by thresholding the statistical cluster size maps from the FA analysis at $p < .05$ (corrected) and then nonlinearly deproject the clusters back to raw DTI space of each participant. The individually back-projected clusters were used as masks on the λ_1, λ_2 and λ_3 volume of each participant and then calculating principal (λ_1) and radial ($[\lambda_2 + \lambda_3]/2$) diffusivity in this region for each subject.

Associations between behavioral measures from the Flanker Task, and DTI and ERP indices, respectively, were tested using Pearson's correlations.

Paper II

Voxel-based DTI analyses were performed using permutation-based inference (Nichols and Holmes 2002) as implemented in randomise. We tested for linear and quadratic effects of age on FA, MD, and RD by fitting GLMs to each voxel in the skeleton while allowing sex to covary. 5000 permutations were performed for each contrast, and Threshold-Free Cluster Enhancement (Smith & Nichols, 2009) was used for thresholding. Statistical p-maps were thresholded at $p < .05$, fully corrected for multiple comparisons across space.

Curve fitting of DTI metrics collected from regions and tracts of interest was performed using functions freely available through the statistical environment *R* (http://www.r-project.org/). First, we fitted data by ordinary least-square (OLS) regressions in order to enable comparisons with previous studies and to demonstrate and establish nonlinear relationships with age. Second, fitting was made by locally weighted polynomial regression (LOESS, or locally estimated scatterplot smoothing) (Cleveland & Devlin, 1988). This procedure was used because we wanted to be able to delineate age-related white matter changes without enforcing a common parametric function (e.g. a linear, quadratic or any other higher order polynomial functions) on the full dataset as is the case with OLS regressions. Briefly, in LOESS a polynomial fit is made iteratively on a subset of the data in a moving fashion. For the fit at age X, the fit is made using values in a neighborhood of X, each weighted by the distance from X. The size of the neighborhood is defined by alpha, and for alpha < 1, the neighborhood includes a proportion alpha of all values (i.e. ages). Here, data was fitted in four iterations with alpha set to 0.75. Observed and fitted values of FA, MD, RD, and standardized residuals of WM volumes after regressing out estimated intracranial volume (Buckner et al., 2004) were plotted as a function of age to visualize the age-related variability and predicted trajectories. Sex was regressed out in all analyses.

To explore the spatial variability in white matter maturation and aging, we performed robust LOESS (rLOESS, which ignores outliers based on certain criteria including the standard deviation from the mean at each point X) fitting on each voxel in the skeletonized FA volume using custom-made Matlab® functions. Age at maximum estimated FA was recorded for every voxel and mapped back to the skeleton. Also, the age when FA equalled the value corresponding to 50 % of the distance between maximum FA and FA at maximum

age was estimated and mapped back to the skeleton. Hence, every skeleton voxel was represented age at maturational plateau and age at 50 % of total estimated age-related reduction. This enabled us to create time-lapse movies of the spatiotemporal dynamics of the maturation and aging of DTI indices (see Paper II, Supplementary Movies).

LOESS is but one of various curve fitting techniques which all share the benefit of not enforcing a common parametric function on the observed data. We have recently successfully applied the same approach (rLOESS) to various indices of cortical gray matter imaging indices (Westlye et al., 2010a) and a related non-linear curve fitting algorithm (the smoothing spline) to hippocampal volume data (Fjell et al., 2010).

Paper III

Median reaction time for each subject in the various ANT cue and target conditions were correlated (Pearson's r) with age to explore the age dependency on the absolute reaction time measures. We tested for main effects of sex on reaction time using independent samples t-test. Next, we correlated the ANT component scores with age within and across genders (partialling out sex in the latter). Effects of sex on the age correlations were tested using Fischer's Z-tests. To explore the relationships between the different ANT components, we correlated each of the composite scores before and after partialling out sex and age. In order to test for relations between the experimental indices of attentional function to more general intellectual abilities, we correlated each of the ANT scores with full scale IQ as measured by all four subtests of WASI while partialling out age and sex.

Brain-behavior relationships were tested across the brain surface by fitting a GLM of the effect of ANT scores on thickness in every vertex across the surface. Since age is negatively associated with cortical thickness in adults (Fjell et al., 2009; Salat et al., 2004; Westlye et al., 2010a), we included age and sex as covariates in the statistical models. All variables were mean centered prior to analyses. Since age, unsurprisingly, was found to be a strong predictor of reaction time across conditions, we performed the analyses on ANT scores adjusted for reaction time in relevant baseline conditions in order to control for age-related global slowing. We performed separate analyses for executive control, alerting, and orienting to explore common and unique relations to cortical thickness across attentional functions. Performance on most specific cognitive tasks used within the cognitive neurosciences might be confounded by general intelligence. Therefore, if researchers are primarily interested in the brain areas underlying a specific ability, it might be helpful to statistically control for general

intelligence to isolate what is unique to a single task (Deary et al., 2010). Thus, we tested for possible modulating effects of general intellectual functions on the brain-attention correlations by including full scale intelligence quotient (FSIQ) as an additional covariate in multiple linear regressions with age, sex, and ANT composite score as independent variables and cortical thickness as dependent variable. Specifically, we tested whether including FSIQ in the model influenced the statistical relationship between thickness and ANT.

To explore the stability of the brain-behavior correlations throughout the adult lifespan, we tested for possible age × ANT score interactions on cortical thickness by including the interaction term as an additional covariate in multiple linear regressions with mean cortical thickness within the significant clusters revealed by the main effect analysis as dependent variables. To validate and further explore the stability of the brain-behavior relationships, we divided the full sample into two age groups by splitting the full sample at median age and then calculated the brain-behavior correlations in the significant effect sites from the full-sample analysis within each age group. Since one could argue that age-related heteroscedasticity (i.e. increasing variability with aging) may influence the brain-behavior associations, we compared the variability in each of the measures between the two age groups. Specifically, we computed the relative coefficient of variation (rCoV) in cortical thickness in the effect sites and compared between groups. rCoV was defined as ([100 × SD]/mean) and was computed for each group separately. Since rCoV is not suited for variables that are not always positive, we computed the standard deviation for each of the attention components and compared between groups.

To reduce the probability of Type I errors, cortical thickness analyses were corrected for multiple comparisons using cluster size inference by means of Z Monte Carlo simulations as implemented in FreeSurfer (Hagler et al., 2006; Hayasaka & Nichols, 2003). Here, clusters were tested against an empirical null distribution of maximum cluster size built using synthesized Z distributed data across 10 000 permutations, yielding clusters fully corrected for multiple comparisons across the surface.

RESEARCH ETHICS

All research performed during the course of this project has been carried out according to the Helsinki declaration. We have strived towards and have gone to great lengths to ensure proper ethical treatment. Written and verbal informed consent has been obtained from all participants prior to the examinations. All parts of the project have been reviewed and approved by the Norwegian regional committee for research ethics (REK-Sør) and the Norwegian Social Science Data Services. All participants have been given a reasonable compensation for their time, transport, etc.

Magnetic resonance images from all participants have been evaluated by a specialist in neuroradiology. When conditions have been discovered that have been deemed necessary to follow up, this has been arranged through the relationship with Oslo University Hospital, Rikshospitalet. Most researchers involved in the present project are authorized clinical psychologists and thus legally obliged to follow the Norwegian Health Personnel Act. All research activities have been performed accordingly to ensure each participant's personal integrity and health.

All data used in the present thesis have been available to all members of the core research group. Data analysis, interpretations and quality assessments have been performed in an open and collaborative environment to ensure proper handling.

SUMMARY OF PAPERS

PAPER I

White matter is critical to cognitive function and brain activity. The objective of the present study was to test whether diffusion tensor imaging derived white matter measures are related to the event-related potential error-related negativity. 87 healthy middle-aged adults underwent diffusion tensor imaging and electrophysiological recordings while performing a version of the Eriksen flanker task. The error-related negativity was elicited in error trials. Fractional anisotropy was calculated based on the diffusion tensor imaging scans. Fractional anisotropy indexes degree of anisotropic diffusion in every voxel, and is assumed related to the integrity of myelinated fiber bundles. The principal neuronal generator for the error-related negativity is located in the anterior cingulate cortex. Hence, the relationship between fractional anisotropy in the cingulum bundle and the amplitude of the error-related negativity was tested. It was found that fractional anisotropy in the left posterior cingulate correlated with the error-related negativity. Eigenvalue analyses revealed that radial diffusivity was responsible for the effect. The amplitude of the error-related negativity correlated with response accuracy in the Flanker task, suggesting that electrophysiological measures are intermediate explanatory variables connecting diffusion tensor imaging indices of white matter organization, synchronization of large cell assemblies, and behavior.

PAPER II

Magnetic resonance imaging volumetry studies report inverted U-patterns with increasing white-matter volume into middle age suggesting protracted white matter maturation compared with the cortical gray matter. Diffusion tensor imaging is sensitive to degree and direction of water permeability in biological tissues, providing in vivo indices of white matter microstructure. The aim of this cross-sectional study was to delineate age trajectories of white matter volume and diffusion tensor imaging indices in 430 healthy subjects ranging 8-85 years of age. We used automated regional brain volume segmentation and tract-based statistics of fractional anisotropy, mean, and radial diffusivity as markers of white matter integrity. Nonparametric regressions were used to fit the age trajectories and to estimate the timing of maximum development and deterioration in aging. Although the volumetric data supported protracted growth into the sixth decade, diffusion tensor imaging

indices plateaued early in the fourth decade across all tested regions and then declined slowly into late adulthood followed by an accelerating decrease in senescence. Tractwise and voxel-based analyses yielded regional differences in development and aging but did not provide ample evidence in support of a simple last-in-first-out hypothesis of life-span changes.

PAPER III

Efficient attention is pivotal for cognitive functioning, and individual differences in attentional functions are likely related to variations in structural properties of the brain. Attention is supported by separate processes, and models of the relationship between attention and brain structure must take this into account. The Attention Network Test (ANT) yields behavioral measures of three independent attentional components: executive control (EC), alerting, and orienting. EC relates to resolving cognitive interference, alerting refers to continuous maintenance of a vigilant state, and orienting to selection of and orienting toward sensory information. Evidence from functional neuroimaging studies suggests that the ANT components recruit different cortical networks. However, the structural correlates are not established. Therefore, ANT scores were correlated with cortical thickness across the brain surface in 268 healthy adults spanning 20-84 years of age. Specific correlations were found between cortical thickness and EC and alerting in regions implicated by functional neuroimaging and lesion studies, including anterior cingulate, lateral prefrontal, and right inferior frontal gyri for EC and parietal areas for alerting. The brain-behavior correlations were relatively stable across adulthood, indicating that factors influencing cortical maturation rather than aging-related atrophy specifically were instrumental in shaping the structural foundation for visuospatial attention in adults.

DISCUSSION

Any inference made from the cognitive neurosciences will only be as valid as our ability to measure psychological, brain structural or functional phenotypes validly and specifically (Green et al., 2008). Parsing the components of cognitive functions requires well-defined behavioral tests to ensure that the components under investigation are actually being measured. To this end, psychological theory and rigorous psychometrics are imperative (Green et al., 2008).

All participants in the present project have been assessed using validated and standardized neuropsychological and computer-based tests designed to measure specific cognitive operations. In Paper I and Paper III in the current thesis we present brain structural correlates of two widely used behavioral paradigms assumed to tap various forms of attentional and cognitive control mechanisms. In Paper I we also include an electrophysiological marker of large-scale integration of neuronal signalling related to error processing and behavioral monitoring.

In the following, the results from the presented papers will be discussed in light of existing knowledge about the workings of the brain, cognitive models, and theories of neurocognitive aging.

RELATIONSHIPS BETWEEN WHITE MATTER MICROSTRUCTURE AND AN ELECTROPHYSIOLOGICAL MARKER OF ERROR PROCESSING AND BEHAVIORAL MONITORING

In a rapidly and continuously changing environment, goal-directed behavior requires monitoring and dynamic adjustment of ongoing actions. Errors are highly informative for the organism for successful adjustments of behavior (Debener et al., 2005; Ridderinkhof et al., 2004). Accordingly, neuronal correlates of error processing and performance monitoring have been investigated intensively by means of electroencephalography and functional magnetic resonance imaging. It has long been known that errors in speeded response tasks elicits a characteristic event-related potential termed the error-related negativity (Gehring et al., 1993). In Paper I, we employed a version of the Eriksen Flanker Task (Eriksen & Eriksen, 1974), which is a widely used paradigm in studies of cognitive interference and control. The task yields reaction time indices of the degree of cognitive conflict, and thus produces behavioral

data assumed to reflect the efficiency of the cognitive processes involved in resolving the interference. The most basic measure is the difference in reaction time between a set of congruent and incongruent stimuli. Increased reaction time in the incongruent condition is assumed to reflect the time needed to resolve the cognitively conflicting stimuli, and is thus used to index the degree and efficiency of cognitive control. The task is a speeded response task, and reliably produces erroneous responses.

The main aim of the study presented in Paper I was to measure the electrophysiological potentials immediately following such erroneous responses, and relate the strength of this response with white matter microstructural properties and behavior as measured from the Flanker Task.

The shape of the ERN component is characterized by a sharp negativity in the electrical potential following commission errors, usually peaking 40-70 ms after the erroneous response (Falkenstein et al., 2000; Taylor et al., 2007). The ERN is generally assumed to reflect cognitive processing associated with errors in speeded response tasks. The exact neurocognitive and neurobiological underpinnings of the ERN is not fully understood, but available evidence suggests that ERN partly reflects cognitive control mechanisms involved in monitoring processes (Bush et al., 2000; Falkenstein et al., 2000) and detection and processing of conflict and errors (Yeung et al., 2004). ERN likely also reflects reinforcement processes initially executed in dopamine-rich striatal areas (Schultz et al., 1997), in particular in response to prediction errors (Holroyd & Coles, 2002; Holroyd et al., 2006; Holroyd et al., 2003; Nieuwenhuis, Holroyd, et al., 2004; Nieuwenhuis, Yeung, et al., 2004). ERN might therefore serve as a electrophysiological marker of brain processes related to fundamental learning mechanisms (Frank et al., 2005).

Several studies have pointed to the involvement of the cingulate in error processing and in the generation of the ERN (Mathalon et al., 2003; van Veen & Carter, 2002, 2006). By applying source localization of ERP data, Herrmann et al. (2004) pinpointed the neural source of the ERN to the anterior cingulate cortex. Further more, by recording concurrent functional magnetic resonance imaging and electroencephalography, Debener and colleagues (2005) documented converging evidence of cingulate involvement in error processing in participants performing a similar version of the Flanker task as we used in Paper I. In addition to the generator in the cingulate gyrus, evidence from lesion studies point to distributed cortical and subcortical involvement in ERN which indicates that the integrity of the underlying white matter contributes to the error related potentials (Gehring & Knight, 2000; Hogan et al., 2006; Stemmer et al., 2004; Ullsperger & von Cramon, 2006).

Advances in neuroimaging methods have recently made it possible to map the organization and strength of brain wiring *in vivo.* For example, diffusion tensor imaging is sensitive to the direction and degree of water displacement in biological tissues (Beaulieu, 2002; Le Bihan, 2003). As discussed above, diffusion of water molecules in brain parenchyma is restricted by cytoskeletal axonal elements such as the plasma membrane, microtubules and myelin sheaths (Beaulieu, 2002). Since water diffuses faster along than across the axon, DTI enables detailed depiction and quantification of the local organization of white matter bundles wiring the cerebral neuronal circuitry (Mori & Zhang, 2006).This technique has motivated a rapidly growing interest in disconnection models proposing that white matter structural connectivity modulates e.g. symptoms in various psychiatric disorders (K. L. Davis et al., 2003; Kubicki et al., 2005; Kubicki et al., 2003; Kyriakopoulos & Frangou, 2009; Lim & Helpern, 2002), and might also be sensitive to structural variability underlying individual differences in cognitive function (Bennett et al., in press; Charlton, Barrick, Lawes, et al., 2010; Charlton, Barrick, Markus, et al., 2010; Grieve et al., 2007; Johansen-Berg, 2010; Madden, Spaniol, et al., 2009; Madden et al., 2004; Sullivan et al., 2008; Tuch et al., 2005; Zahr et al., 2009).

The proposed neurocognitive *sensitivity* of DTI rests on the assumption that diffusion characteristics in the brain reflect important features of the microstructural integrity of the biological tissue. DTI might therefore be predictive of variability in the structures necessary for efficient transmission of electrochemical signals and thus for neuronal communication (Dubois, Dehaene-Lambertz, Soares, et al., 2008; Stufflebeam et al., 2008). However, although the potential of DTI has been widely acknowledged, very little is known about the relation between DTI properties and other imaging indices of brain function.

Also, little has been known about the neurocognitive *specificity* of DTI indices. While several reports have documented relatively specific associations between DTI and cognitive functioning (Charlton, Barrick, Lawes, et al., 2010; Charlton, Barrick, Markus, et al., 2010; Kennedy & Raz, 2009; Niogi et al., 2010), it has been argued, although not without controversies (Charlton, Landau, et al., 2010), that the DTI indices of white matter integrity is more related to general intellectual abilities or a common *g* factor than to the aging of specific neurocognitive functions (Penke & Deary, 2010). The main aim of Paper I was thus to test the hypothesis of a specific relationship between the strength of the scalp recorded ERN, which partly reflects the large-scale synchronization and integration of activity in large cell assemblies (Varela et al., 2001), and the microstructural properties of the underlying white matter in relevant areas as indexed by DTI.

The results from Paper I indeed supported a positive relationship between white matter integrity in posterior parts of the cingulum bundle and the strength of the ERN, and thus provided evidence of a link between the amplitude of a cognitive electrophysiological component and diffusion tensor imaging. In particular, the degree of diffusion anisotropy in a cluster of voxels in the posterior part of the left cingulum bundle (please see Paper I, Figure 6) was related to the amplitude of the ERN, indicating that individuals showing the strongest electrophysiological responses to errors also showed the highest degree of anisotropy in this area. These results point to the importance of white matter properties in the posterior part of the cingulum for the ERN amplitude measured on the scalp, which supports the notion of regional specificity of brain-behavior associations.

Functional imaging and source localization studies converge on a more anterior distribution of the neuronal generators for the ERN (Debener et al., 2005; Herrmann et al., 2004). However, it is very likely that axons in the posterior cingulum project towards anterior parts of the cingulate gyrus (Schmahmann & Pandya, 2006), and as such instantiate a structural and functional network comprising anterior and posterior parts of the cingulum bundle. To test this hypothesis by means of diffusion tensor imaging data, we have performed probabilistic fiber tracking (Behrens et al., 2007; Behrens, Johansen-Berg, et al., 2003; Behrens, Woolrich, et al., 2003) using the voxels in the significant cluster in the posterior parts of the cingulum as seeds. Figure 13 shows the resulting reconstructed white matter pathways in 20 representative individuals. It is seen that the areas showing significant associations with ERN amplitude propagates towards anterior parts of the cingulum bundle. This partly validates our assumptions discussed in Paper I, namely that the cluster is part of a functional network comprising anterior parts of the cingulate. Thus, it is likely that compromises to the white matter integrity in any part of this network might influence the working of the associated cortical areas, although not necessarily in the immediate proximity. This is an interesting finding which points to the importance of investigating brain-behavior relationships within the framework of functional networks.

Further, we found that ERN amplitude statistically predicted response accuracy in the Flanker task, but no correlation between DTI and behavior was found in the cingulum. This might suggest that electrophysiological measures serve as an intermediate explanatory variable linking DTI indices of white matter microstructure, large-scale integration of brain activity, and behavioral variability, i.e. cognitive function. Interestingly, one previous study combining functional MRI, DTI and behavior reported that white matter integrity did not mediate age-related increases in frontoparietal activation during a visual attention task

(Madden et al., 2007), indicating that the relationships between DTI and functional imaging measures are far from simple. Although we believe our findings of an association between the amplitude of the error-related negativity are encouraging, further studies exploring the links between brain structure, electrophysiology and cognition are warranted.

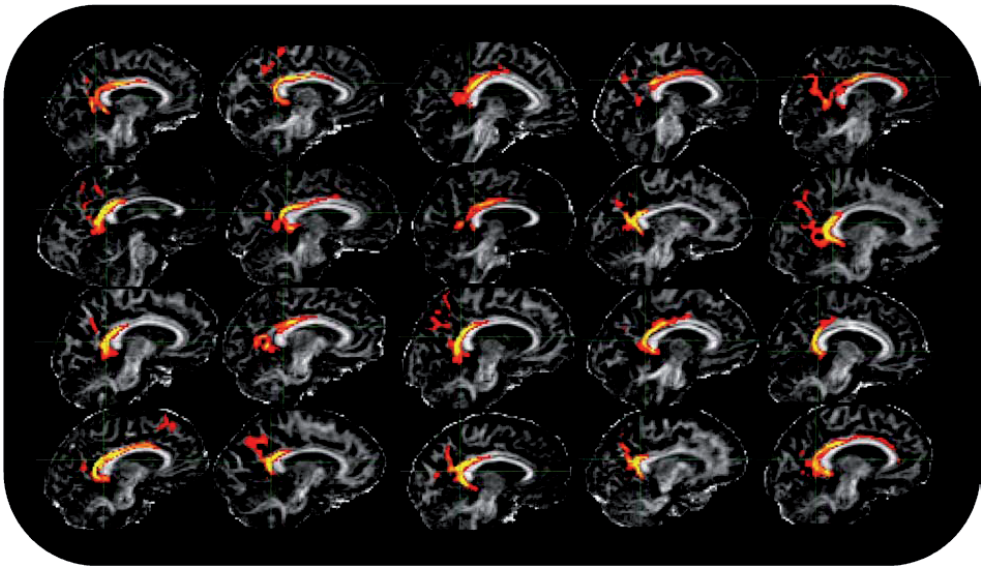

FIGURE 13: Probabilistic fiber tracking validates localization of effects. The cluster in posterior parts of the cingulum bundle showing significant associations with ERN was used as seed voxels (Westlye et al., unpublished). The figure shows the results from 20 representative participants.

MACRO- AND MICROSTRUCTURAL ALTERATIONS OF THE HUMAN BRAIN WHITE MATTER THROUGH THE LIFESPAN

The human brain undergoes significant changes throughout life. For example, at the age of 20, the brain has a total myelinated neural fiber length of about 160 000 km (Marner et al., 2003). By the age of 80 this has been reduced by almost 50 % (Marner et al., 2003). A fundamental task of the neurosciences is to track and understand the mechanisms responsible for these structural changes, the functional and cognitive consequences and its relations to disease.

Neuronal structural connectivity is a basic feature of brain organization (Geschwind, 1965), and researchers studying human brain function have increasingly realized the importance of connectivity data to unravel the mystery of the mind in aging and disease. What are the functional and cognitive consequences of structural breakdown in aging? Are the same factors underlying brain connectivity changes also controlling cognitive functions and paving the pathways toward cognitive deterioration and disease? When does the brain stop maturing and start aging?

The final sample in Paper I was restricted to healthy adult participants within a relatively narrow age range (40-60 years). Although the inter-individual variability is large, aging is generally associated with cerebral structural alterations (Walhovd et al., 2005) and cognitive decline (Salthouse, 2009), even in absence of neurodegenerative disease. Delineating normal life span development of human brain function and structure provides important knowledge about the normal alterations associated with development and aging, but might also inform studies of the pathophysiology of developmental and neurodegenerative disorders. It has indeed been proposed that by identifying the trajectories of normal brain alterations throughout life, we might provide an Archimedean point from which to interpret and understand the aberrant pathways observed in disease (Tau & Peterson, 2010). Thus, characterizing the mechanisms underlying normal variation is indispensible for the understanding of disease.

Recent advances in magnetic resonance imaging methodologies have enabled detailed analysis of the aging-related cortical gray matter loss as indexed by cortical thinning (Fjell et al., 2009; Salat et al., 2004; Westlye et al., 2010a). It has been known for a long time that subcortical white matter volume decreases with age also (Jernigan et al., 2001; Walhovd et al., 2005), but diffusion tensor imaging have recently enabled more fine-grained analyses of white matter changes occurring with aging. A growing body of evidence converges on decreased microstructural integrity with increasing age (Bennett et al., 2010; S. W. Davis et

al., 2009; Head et al., 2004; Hugenschmidt et al., 2008; Madden, Bennett, et al., 2009; Salat, Tuch, Greve, et al., 2005; Salat, Tuch, Hevelone, et al., 2005; Sullivan & Pfefferbaum, 2006; Westlye et al., 2010b). However, studies have traditionally investigated the age-related effects on DTI indices by comparing two groups of different ages, e.g. a young and an old group. While such an approach yields absolute differences between two age groups, it precludes more sophisticated analysis including investigations of possible non-linear relations with age. Therefore, studies comparing two age groups might provide highly valuable information, but are associated with the significant caveat that inferences are restricted to linear relationships and are highly vulnerable to the age of the sampled groups (Fjell et al., 2010). The volume of the human brain white matter volume tends to show 3-phasic life-span paths with accelerating changes in the earliest and latest phases of life and a relatively stable plateau in early and middle adulthood (Courchesne et al., 2000; Jernigan et al., 2001; Raz et al., 2005). However, it is has not been known to what degree lifespan diffusivity trajectories support the suggested protracted white matter development inferred from volumetric studies. Because evidence indicates that the maturation of the human brain white matter is a slow process that starts in infancy and continues for decades (Giedd et al., 1999; Giorgio et al., 2009; Klingberg et al., 1999; Lebel et al., 2008; Paus et al., 1999; Tamnes, Østby, Fjell, et al., 2010; Østby et al., 2009), investigations into age-related effects through the lifespan should be based on samples including children, adults, and elderly participants (Raz et al., 2005).

The main aim of Paper II was to test the hypothesis of protracted white matter maturation by delineating regional life-span trajectories of diffusivity and white matter volume in a large sample of healthy participants aged 8-85 years using automated whole-brain volume segmentation and tract-based statistics of DTI indices of white matter microstructural integrity. The findings demonstrated that the microstructural maturation in general peaked early in the fourth decade, and we found no evidence of protracted development into middle age. The estimated nonlinear trajectories supported a three-phasic lifespan model with the characteristic accelerating alterations in the earliest and latest part of life with a slow decline from early adulthood into middle age. Importantly, the maturational plateaus of the DTI measures, which were estimated in the early 30s, occurred markedly earlier than the peaks for white matter volumes, which, in line with previous studies, were characterized by quadratic paths peaking in the early 50s. These findings provide novel insights into the lifespan microstructural white matter changes, and strongly support the notion that DTI is sensitive to subtle changes not detectable by macrostructural measures, including volumetry (Hugenschmidt et al., 2008).

As previously emphasized, neurons in the brain are similarly affected by aging as cells in other organs, and suffers from increasing oxidative stress, accumulation of damaged proteins and energy homeostasis (Mattson & Magnus, 2006). However, it is important to note that the neurobiological mechanisms causing diffusivity changes in brain tissue during maturation and aging are not fully understood. Authoritative comparative and histological studies have documented significant alterations of myelin-related processes in aging (Peters, 2002), including accumulation of water-containing balloon-like compartments in the myelin sheaths (Feldman & Peters, 1998; Sugiyama et al., 2002), formation of redundant myelin, splitting of the myelin lamellae and loss of thin myelinated axons (Marner et al., 2003; Sandell & Peters, 2001). Other factors influencing both volume and diffusion measures include alterations of the fiber diameter (Giorgio et al., 2009; Paus et al., 2008).

The notion of aging as a 'neurocatastrophe' (Mattson & Magnus, 2006) may however express a more pessimistic and deterministic view on brain aging than what recent evidence indicates. For example, increased number of oligodendrocytes (Peters & Sethares, 2004), thickening of the myelin lamellae (Peters et al., 2001), and shortening of the internodes (Peters & Sethares, 2003) found in aged subjects are all indicative of remyelination in old age (Lasiene et al., 2009). Further, several studies have documented plastic changes of the structural integrity of the brain in response to environmental demands and motor and cognitive learning (Bengtsson et al., 2005; Draganski et al., 2004; Draganski et al., 2006; Draganski & May, 2008; Haier et al., 2009; Hyde et al., 2009; Scholz et al., 2009; Takeuchi et al., 2010), even in middle aged and elderly subjects (Engvig et al., 2010).

Also, a recent review evaluated the hypothesis that physical activity and exercise serve to protect and enhance cognitive and brain function (Kramer & Erickson, 2007). The authors optimistically concluded that available literature supports the assumption that physical activity enhances cognitive and cerebral function, and might also protect against the development of neurodegenerative disease. The mechanisms through which physical exercise might exert its effects are not fully understood. However, it has been suggested that exercise enhances angiogenesis, synaptogenesis and neurogenesis (in the dentate gyrus), and also to upregulate various neurotrophic factors in the mouse brain (Cotman et al., 2007; Hillman et al., 2008; Vaynman & Gomez-Pinilla, 2006).

Summarized, it is clear that various environmental and experiential variables to a high degree influence the structure of the human white matter (Fields, 2008), and life-span cerebral structural changes are thus manifested through dynamic patterns of neurobiological, including genetic (Chiang et al., 2009; Kochunov et al., in press; Kremen et al., 2010; Thompson et al.,

2001), and environmental (Boyke et al., 2008; Driemeyer et al., 2008; Lenroot et al., 2009; Park & Reuter-Lorenz, 2009; Raz & Rodrigue, 2006; Sowell et al., 2008) interactions, and future studies might succeed in incorporating and isolating the effects of these modulating variables.

STABILITY AND CHANGE IN THE RELATIONSHIPS BETWEEN BRAIN AND COGNITION THROUGH THE LIFESPAN

The plastic and dynamic patterns of brain changes during development and aging suggest that the relationships between cognitive functions and structural integrity of the brain are also dynamic in nature. Therefore, structure-function correlations in adolescence and young adulthood might not parallel those associations identified in older samples, effectively yielding age by structure interactions on brain function and cognition. The putative dynamics of brain-behavior relationships throughout the lifespan begs the question to which degree such correlations in adult samples are caused by early developmental or later atrophy-related variability. For example, Shaw and colleagues (2006) reported differing neurodevelopmental cortical trajectories between groups of highly and moderately intellectual children, respectively, but found that the differences levelled off in late adolescence, i.e. around 18 years of age. This might suggest that relatively early neurodevelopmental events in childhood sculpt the *rate* of intellectual development rather than the ultimate level of adult intellectual functioning.

Narr et al. (2007) reported positive correlations between general intellectual abilities and cortical thickness in healthy young adults aged 17–44 years of age, indicating that the differences putatively originating in early developmental processes are preserved at a later age. Other contrasting results have also been found. For example, positive relationships between cortical thickness and intellectual abilities has been replicated in children and adolescence of 6-18 years of age (Karama et al., 2010). These authors found that young children (6-11 years) and adolescents (12-18 years) exhibited positive associations in the same cortical areas and no statistically significant differences were observed between them. This contrasts our recent findings of negative correlations between cortical thickness and various cognitive functions in children and adolescents (Tamnes, Østby, Walhovd, et al., 2010).

Findings from a recent longitudinal study of young adults suggested that distinct genetic factors influence the rate of change in cortical thickness and the absolute cortical

thickness in the same regions, respectively (Brans et al., 2010). Importantly, the genetic factors controlling the rate of change were also found to control level of intelligence, emphasizing the importance of including longitudinal data when attempting to uncover brain-behavior relationships (Van Petten et al., 2004). The latter point is also supported by recent findings of an association between rate of cortical thinning in regions of the temporal lobe during a 6 months period and change in memory performance in healthy elderly participants (Murphy et al., 2010).

Interestingly, by analyzing data from 11 000 twins, it was recently shown that the heritability of general cognitive abilities increased linearly from 41% in childhood (9 years of age), 55 % in adolescence (12 years of age) and 66 % in young adulthood (17 years of age) (Haworth et al., 2010). In contrast to what is commonly assumed about the cumulative nature of environmental impacts on psychological phenomena, these findings suggest that genetic variability explains a larger proportion of the variance in intelligence in young adults than in children. That is, the impact of our genetic makeup increases with age, at least during our forming years. Further, it suggests that the specific genes or the interaction between different genes affecting cognitive functions change as a function of age. As emphasized by the authors of this study, the increasing genetic impact of intellectual abilities during neurodevelopment must to be understood in light of the maturation of the probably wide array of brain processes that mediate genetic effects on intelligence (Haworth et al., 2010). The dynamic interplay between genetic and environmental factors producing individual differences in other cognitive functions during development are not known, and whether the degree of the genetic impact stabilizes at one point or continues to fluctuate later in life remains elusive. These important results add to the complex picture of the putative neurobiological factors causing individual differences in cognitive functions in a lifespan perspective, and contribute to the inconclusive picture of brain-cognition association through the lifespan.

Taken together, existing evidence indicate that early maturation of the cerebral cortex modulates the development of general cognitive skills, but it has been unclear to which degree these developmental events affects the *rate* of cognitive maturation or rather the intellectual potential, i.e. the level of adult functioning in the same subject. The developmental perspective, i.e. that maturational neurobiological perturbations determine the adult level of functioning, suggests that the brain–behavior correlations should be relatively stable throughout the healthy adult lifespan. An alternative hypothesis predicts that variability due to aging-related cortical atrophy in higher age is the main force driving the relationships in adult samples. This has been referred to as a neuropsychological perspective (Van Petten, 2004).

Although originally used to explain correlations between hippocampal volume and memory functioning, this view would in general predict positive correlations between brain structural integrity (e.g. cortical thickness) and cognitive functions in elderly participants, but not necessarily in younger. Further, such correlations should become more positive as the age of the sample increases. In her meta-analysis of studies relating hippocampus volume to memory function, Van Petten (2004) found evidence supporting both the developmental and neuropsychological hypothesis in that the volume–memory correlations tended to grow more positive as the age of the sample increased. This indicates that aging-related hippocampal atrophy might play a predominant role in producing structure-function correlations in adults. Importantly, increased between-sample variability in the volume–memory correlations with age was reported, which suggests a complex and seemingly non-stationary interplay between brain and cognition throughout the lifespan.

We have previously shown substantial cortical thinning throughout the lifespan from eight years of age (Westlye et al., 2010a). Interestingly, cortical thinning in development and aging are caused by different neurobiological processes. Maturational cortical thinning is partly explained by use-dependent elimination of synaptic contacts ('pruning') (Bourgeois & Rakic, 1993; Huttenlocher & Dabholkar, 1997; Rakic et al., 1994) with concurrent reduction in glial cells (Paus et al., 2008). Further, myelination of the peripheral neuropil could interact with the MRI contrast, yielding an *apparent* thinning of the cortex due to altered signal intensity and tissue contrast with subsequent tissue misclassifications (Sowell et al., 2001; Westlye, Walhovd, Dale, et al., 2009).

The typical interpretation of adult cortical thinning is that degenerative processes including shrinkage of large neurons (Terry et al., 1987), loss of myelinated axonal fibers (Nairn et al., 1989), deafferentation (Bertoni-Freddari et al., 2002), and reduction in synaptic density (Morrison & Hof, 1997) causes a shrinkage of the cortical ribbon. Accordingly, thinning of the cerebral cortex in aging is usually associated with decreased cognitive function (Dickerson et al., 2008).

The choice of cortical thickness as the phenotype for cortical integrity might be especially beneficial in comparison with other structural imaging phenotypes. In a recent twin study, it was shown that both cortical thickness and surface area were highly heritable, but that they were essentially unrelated genetically (Panizzon et al., 2009). This demonstrates that cortical volumetric studies confound two sources of information that are genetically independent and may be related to cognitive variability in very different ways. The results were recently replicated in a study exploring the genetic contribution to brain volume, grey

matter volume, cortical thickness and surface area (Winkler et al., 2010). All imaging measures were significantly influenced by genetic factors, but cortical thickness and surface area were found to be genetically and phenotypically independent. Importantly, brain volume was more closely associated with surface area than thickness, suggesting that "*surface area and cortical thickness measurements should be considered separately and preferred over gray matter volumes […]* " (Winkler et al., 2010, p. 1135).

Summarized, existing evidence in general converges on a positive relationship between brain integrity, including cortical thickness, and non-specific cognitive abilities, but little evidence have been produced linking variability in cortical thickness to experimentally parsed cognitive functions beyond that captured by intellectual abilities. Further, to which degree such associations between brain structure and cognition in adult samples are driven by neurodevelopmental or aging-related events, has remained elusive.

In Paper III, we sought to investigate these questions by combining behavioral and magnetic resonance imaging data obtained from 263 healthy adults 20-85 years of age and 1) correlate three experimentally measured attentional functions derived from the widely used Attention Network Test with cortical thickness across the brain surface and 2) to test whether the observed associations between attention and regional cortical thickness differed between young and middle aged/elderly adults.

The efficient utilization of available contextual information in the control of behavior and cognition is a core function of the attentional systems. The anatomical basis subserving attentional processing has been defined in terms of localized yet large-scale neuronal networks shown by neuroimaging studies to be recruited during attention-demanding tasks and cortical and subcortical circuits producing specific attentional deficits when compromised (Mesulam, 1981, 1999; Posner & Petersen, 1990). As detailed above, multimodal studies utilizing the ANT have yielded strong predictions of which cortical regions might be recruited by the various attentional networks. The ANT networks thus serve as excellent models when attempting to map the regional correlations between cortical thickness and specific cognitive functions.

Our neuroanatomical hypotheses in this study were informed by previous lesion and functional imaging studies. However, associations between functional and structural imaging indices of age-related decline and cognition are complex (Persson et al., 2006). For example, changes in cortical thickness after cognitive training are not necessarily associated with regionally corresponding functional changes as shown by functional MRI (Haier et al., 2009).

Also, it is well known that functional imaging studies alone cannot establish that a brain area is necessary for a particular cognitive process (Fellows & Farah, 2005) and converging evidence from various lines of research, including lesion and structural and functional imaging studies, are therefore highly valuable.

The developmental and neuropsychological hypotheses are not mutually exclusive. Nevertheless, exploring the stability of the correlations between thickness and attentional functions throughout the adult life span would provide an indirect test of the hypothesis that aging-related atrophy drives the correlations. According to his view, the relationships between thickness and attention are strongest in elderly where accumulated atrophy is largest and weaker in young adulthood and middle age where less aging-related structural alterations are seen (Van Petten, 2004). An increase in the relationships between attentional functions and cortical thickness with increasing age could be taken to support the neuropsychological perspective. In contrast, stable correlation from the earliest part of adulthood throughout middle age and old age would suggest that the correlations are caused by factors influencing cortical thickness at an early stage, that is, neurodevelopmental processes.

The results from Paper III demonstrated regionally specific correlations between cortical thickness and the executive control and alerting components of the ANT. The effects were localized in regions anticipated from earlier functional neuroimaging and lesion studies. The areas included the anterior cingulate cortex for the executive control component and frontoparietal areas for alerting. As previously emphasized, specific cognitive functions might be confounded by general intellectual abilities, and statistical controlling for intelligence might help isolate the uniqueness of the single task (Deary et al., 2010). Importantly, we found that the thickness-attention correlations were found independently of general intellectual abilities. Thus, specific cognitive tests might help identify brain networks related to cognitive abilities beyond a general intelligence factor (Haier et al., 2010). These findings were in agreement with our expectations, and further support the neurocognitive specificity of measures of regional cortical thickness as a valid imaging phenotype.

The correlations between thickness and attention were relatively stable throughout the adult lifespan. This might suggest that the associations were at least partly originated in neurodevelopmental processes rather than aging-related cortical atrophy. To the degree that our results showed converging evidence of regional correlations between cortical thickness and attentional functions, the results presented in Paper III strengthens the notion of specific involvement of functional cortical networks in the executive and alerting component of attention. However, while such findings might be taken as a proof-of-principle of regional

involvement in specific cognitive functions, interpretation of the present results must be done with caution, as the relationships between structural and functional brain measures are complex, particularly in a life span perspective.

As discussed above, further progress in the study of the functional and structural organization of the human brain is dependent upon an expansion of the psychological sciences to include a science of behavior in addition to a science of the brain (Cacioppo & Decety, 2009). Importantly, findings from the cognitive neurosciences might provide clues as to which brain properties are important for producing differences between individuals in intellectual abilities or more specifically assessed cognitive or motor functions. However, the psychological or mental construct (e.g. intelligence, diagnosis or cognitive function) one aims to explain by imaging derived properties of the brain are always dependent on how one chooses to define, operationalize and measure the construct. For example, an individual diagnosed with disease X using one specific diagnostic tool might not fulfil the criteria used in another diagnostic tool. Thus, the same person might fall into different diagnostic categories depending on the specific diagnostic tool the researcher chooses to use. Similarly, an individual might be characterized as highly intelligent by one test, but below average on another test. Thus, the construct the researcher is focusing on (e.g. diagnosis, intelligence, etc) is always closely related to how the construct was defined and measured. Although this is an inherent limitation to all research implying some kind of assessment or measurements, it might be particularly relevant when aiming to make inferences about psychological phenomena like memory or emotions than more physical constructs like the height or weight of an individual. Importantly, this does not necessarily imply that such constructs are more "real" than psychological phenomena, just that they are more easily accessible to the researcher.

In cognitive neuroscience, the researcher is often aiming to make inferences about the associations between mental operations and the workings of the brain. Psychological constructs are often defined in terms of modular flowcharts and metaphors (e.g. the "visual sketchpad" of the working memory), which in terms of conciseness and complexity usually are far away from the physical operations carried out by the neurons in the brain. Thus, researchers often adhere to circular definitions and interpretations of their results when trying to explain how the brain enables the individual to solve everyday problems. For example, we infer that the neurons are engaged in something we might call "cognitive control" because some parts of the brain show certain response patterns when we tell the individual to perform a "cognitive control task".

The challenges related to the translation between the psychological phenomenology and the physical reality of the brain is fundamental to the cognitive neurosciences in general and in particular to studies aiming to understand the link between the human mind and the workings of the brain (Cacioppo & Decety, 2009). In the present thesis, we have aimed to minimize the concerns related to this translation by implementing behavioral tasks developed according to cognitive theory and validated using various approaches, and thus representing putatively valid cognitive phenotypes. However, research incorporating data from several scientific levels of enquiry will always have to consider the idea that the different levels might not speak the same language. Thus, future progress towards the integration of the cognitive sciences, psychology and neuroscience into a common converging framework relies on the successful incorporation of sophisticated psychological theories and models in combination with an increasing appreciation of the potentials and limitations imposed by the physical reality of the brain.

CONCLUSIONS

PAPER I

The amplitude of the error-related negativity is associated with diffusion tensor imaging indices of white matter microstructure in posterior parts of the left cingulum bundle. This provides evidence for a direct link between the functional integration of large-scale neuronal networks and the underlying structural connectivity, and supports the use of diffusion tensor imaging as an imaging phenotype of the structural variability underlying efficient neuronal transmission and synchronization.

PAPER II

Diffusion tensor imaging indices of microstructural integrity in general show maturational plateaus in the late 20s and early 30s, decades before the estimated maxima of the regional volumes of white matter. This demonstrates that diffusion tensor imaging is sensitive to neurobiological changes not detected by volumetry, and therefore adds to the putative clinical utility of diffusion tensor imaging. The close association between age and diffusion tensor imaging indices supports the use of diffusion tensor imaging as an imaging phenotype in the study of the neurobiology of the aging brain.

PAPER III

Regional cortical thickness in relevant regions is specifically associated with the attentional networks derived from the Attention Network Test, beyond what can be attributed to general intellectual functioning. Further, no evidence of significant age by function interactions on cortical thickness was found, suggesting that the regional correlations between cortical thickness and attention were comparable for younger and older participants. This might indicate that relatively early neurodevelopmental events, and not aging-related accumulation of cortical atrophy, sculpt the brain structures involved in attentional functions. The regional specificity of the associations indicates that cortical thickness is both a sensitive and specific imaging phenotype.

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